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they can live

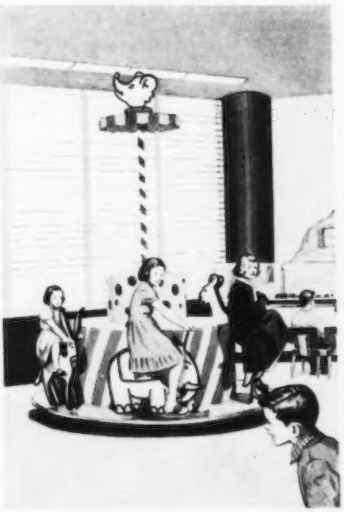
In children less than 15 years of age, there occur certain forms of neoplasms not found in adults. Medulloblastoma is seen only in children, malignant neurocytoma only in infants. Most tumors of infants are of strictly embryonal type and many are of complex teratoid structure. Adult types of tumors in children metastasize earlier and more widely and run a more rapid course than in adults.

Malignant neoplasms in childhood have a generally poor prognosis. However, recent advances in diagnosis and therapy are increasing the rates of cure in some types. In other types such as leukemia the outlook remains hopeless, although worth-while remissions are induced in a significant number of patients.

Present results in the management of neoplasms in children give hope for further increased survival rates from earlier diagnosis and improved treatment. More effective therapy may be expected from research now in progress; earlier diagnosis can only be achieved by co-operation of parents and physicians.

The recent increasing interest in child health and welfare is yielding a general, steady decrease in infant mortality rates, especially from communicable disease. Mortality rates from neoplastic disease, on the other hand, have gone up. More children between the ages of 2 and 14 years now die of cancer than of any other disease.

Neoplasms may occur in the fetus, during the neonatal period, or any time thereafter. Detection of tumors sufficiently early for successful treatment requires parents and physician to be on the continuing alert. Constant watch may reveal a change in body contour by a mass, an unusual increase in girth, a suddenly enlarging and ulcerating spot on the skin, a defect in vision, a change in behavior and personality—all signs of possible neoplasm. All solid masses are considered to be malignant until the microscope proves otherwise.



Cover

Leukemic patients under chemotherapy enjoying added years of life at the Children's Cancer Research Foundation, Boston.

NEWSLETTER

MAY, 1953

Children: Dargeon (American Academy of Pediatrics) is completing a statistical survey that should remind physicians again to consider cancer in diagnosing childhood diseases. With new controls for serious and fatal hazards in pre- and postnatal life, the problem of juvenile cancer threatens to increase. Among the more common kinds of childhood cancers are the malignant lymphomas and leukemias, neuroblastoma, retinoblastoma, Ewing's tumor, osteogenic sarcoma, Wilms's tumor, rhabdomyosarcoma, and adenocarcinoma.

Aging: Saxton (Washington U.) found that 18.7 per cent of the 12,443 autopsies conducted during the last fifteen years at St. Louis City Hospital showed cancer and that the incidence was rising (from 16.8 per cent during the first five years to 20.6 in the last five years). Particularly on the rise were cancers of the lung, prostate, and pancreas. Some types of cancer had a characteristic age pattern; and some seemed independent of aging.

Detection Tests: Blood and urine tests keep cropping up in cancer research and little heed is paid them. Far more newsworthy would be confirmation of any of the dozens of tests that have been advanced in the past. Prospects for this are not bright; neither are they utterly hopeless, a recent survey of test-testing centers discloses. Homburger (Tufts), Stowell (Kansas), Sprunt (Tenn.) and Lippincott (Wash.) so far have failed to declare any test of practical value in the early detection of cancer. All of them, however, are convinced that the search should go on. Homburger feels that techniques of value in detecting and diagnosing specific cancer types conceivably could be developed. Lippincott thinks plasma proteins may hold a key to reasonably early detection of some of the hard-to-find internal tumors. Stowell thinks that phenomena cited as cancer indications should be traced down to their source for such light as they may throw on the nature of cancer and other conditions. And Sprunt is encouraged by preliminary tests of the Penn-Dowdy (U.C.L.A.) technique. Preliminary

results still leave the Parfentjev (Yale) test in the ranks of the possibly practical techniques. A growing number of investigators are showing interest in Massopust's (Marquette) findings that simple infrared photographs show up a high percentage of breast cancers. The apparatus is simple and cheap (ordinary photographic material and lighting are supplemented by infrared filters and film). The procedure takes only a few minutes of the patients' and technicians' time. The technique is based upon the fact that infrared rays penetrate about 2 mm. beneath the skin and show the superficial venous pattern clearly. Cancers, including the deep ones, give the veins an engorged appearance and frequently show venous interruptions. Benign tumors have not done this.

Here and There in Research: Trunnell (M. D. Anderson) has been testing patients' sera for their possible therapeutic effect on experimental cancers. One patient produced serum that completely knocked out several types of animal cancers . . . but the patient died of her own breast cancer.

Macdonald (Ian) and others (Univ. South Carolina) have repeated old observations by Lombard and Macdonald (Eleanor) and confirmed their findings that socio-economic status may be related to cervical cancer. Cervical cancer they found commonly among widows, divorcees, women separated from their husbands, and those who married, bore children, and ceased having children early in life.

Mazia (Cal.) has isolated cell "mitotic apparatus." He learned that with detergents he could remove all but the essential chemicals and structures involved in cell division. His purified material offers exciting possibilities in cancer.

Samuels's (Utah) ability to determine chemically the circulating hormones continues to move ahead. The technique now is being applied to normal people and patients with a variety of diseases, including mental conditions.

Pomerat (Texas) and Hsu stumbled on a finding that opens a new door to cancer investigation. A technician forgot to put the right amount of salt into a culture in which human tissues had been grown. The monolayer of cells stretched in the hypotonic solution, affording an extremely detailed microscopic analysis of structures. They found that human cells frequently had one or a few more or less

(Continued after page 124)

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Keeping up

Liver—Needle-Punch Biopsy

At the Coral Gables Veterans Administration Hospital 308 needle biopsies of the liver have been performed on 280 patients. Needle biopsy of the liver is of definite benefit to any patient suffering from primary liver disease as well as any systemic disease in which the liver is involved secondarily. It should be added to the multitude of liver-function tests. Four cases of primary carcinoma and twenty-six cases of metastatic carcinoma of the liver were diagnosed in this way. The method of performing punch biopsy of the liver, its indications, contraindications, and illustrative case reports are given. It now has a definite part in the diagnostic equipment to be used in the differential diagnosis of primary liver disease.

Rumball, J. M.: Needle biopsy of the liver; an analysis of 308 cases. Am. J. Surg. 84:131-140, Aug., 1952.

Breast Self-Examination

How many women continue breast self-examination after instruction and how many breast tumors can be found in this way? Questionnaires were sent to the 470 women to whom personal instruction in breast self-examination had been given. There were 129 replies or a 27 per cent return. Seventy-nine per cent of those reporting after a period of more than eighteen months stated that they had been and were still carrying out the practice of breast self-examination. Of this number, 62 per cent were examining at least once every two months. Breast self-examination taught to this group of 470 women led to the discovery of one malignant and eight benign tumors. There is a very real likelihood that breast self-examination may lead to the discovery of a significant proportion of early breast-cancer cases.

Gowen, G. H.; Hittle, E.; Roe, N., and Crawford, I.: Is teaching breast self-examination for cancer effective? Illinois M. J. 102:179-182, Sept., 1952.

Gastric Cancer—Cytological Diagnosis

The difficulties inherent in the application of cytological methods to the diagnosis of gastric cancer are apparent in the variety of methods advocated. The future usefulness of the cytological technique applied to the diagnosis of gastric lesions depends in great part upon the development of more efficient methods of collecting and concentrating cells. One possibility is mechanical irritation of the gastric mucosa. Another approach to the problem is the search for a chemical irritant that will induce desquamation without affecting cell stucture. The present authors have been investigating the results to be obtained with papain solutions.

This study is based upon 1000 cases collected from various sources. In 600 patients specimens were obtained by simple aspiration from the fasting stomach or by saline lavage. The second group is made up of 400 cases in which a papain lavage was utilized. All specimens were examined by the Papanicolaou and Traut procedure. The papain technique was developed because of the authors' dissatisfaction

n with Cancer

with the saline-lavage method. The undesirable side effects of the papain lavage have been few and inconsiderable. Smears obtained by the use of the papain technique were richer in cellular content than when the material was collected by saline lavage. It was apparent that when the tumor body was accessible to the papain solution, the accuracy of the technique was high. As a result of this experience, the authors are convinced that the cytological technique, making use of the papain lavage, is the most promising single approach to the problem of the early diagnosis of gastric cancer.

There would seem to be a possible accuracy of about 85 per cent when papain lavage is utilized. In all but one instance, the use of the papain technique permitted positive diagnosis with only one specimen. Repeat examinations consistently confirmed the original positive finding. The use of papain can go far toward making cytology the diagnostic technique that is required for an effective approach to the problem of gastric cancer.

Traut, H. F.; Rosenthal, M.; Harrison, J. T.; Farber, S. M., and Grimes, O. F.: Evaluation of cytologic diagnosis of gastric cancer. Surg., Gynec. & Obst. 95:709-716, Dec., 1952.

Cancer of the Lung—Early Diagnosis

Successful surgical treatment can be accomplished only if carcinoma is recognized early. It is important that all physicians become aware of cancer of the bronchus and that all diagnostic aids be utilized whenever necessary. Certain groups of symptoms and physical signs such as cough, expectoration, pain, discomfort, dyspnea, and wheezing respiration may suggest carcinoma and should lead to further careful investigation. Roentgen-ray examination of the chest is unquestionably the most important single diagnostic aid in determining the presence of bronchogenic carcinoma. The next procedure in suspected cases of lung cancer is bronchoscopy, which includes visualization of the tumor within a bronchus or of alterations in the bronchial tree, biopsy of the tumor, and collection of secretions for cytological study. Cytological examination of sputum, spontaneously discharged bronchial secretions, and bronchial washings is obligatory. The primary purpose of cytological examination is to make the diagnosis early. In a series of 540 consecutive patients with carcinoma of the lung, the authors have been able to make a positive cytological diagnosis in 476, or 88.3 per cent. In the same series, the bronchoscopic biopsy was positive for carcinoma in 167 patients, or 30.9 per cent. If a positive preoperative morphological diagnosis cannot be obtained, and if the possibility of carcinoma of the lung cannot be ruled out clinically, an exploratory thoracotomy is indicated.

Clerf, L. H., and Herbut, P. A.: Early diagnosis of cancer of the lung. J. A. M. A. 150:793-795, Oct. 25, 1952.

Cancer of the Ear, Nose, and Throat

No other area of the body, except the skin offers a better chance for cancer cure than the ear, nose, and throat. Pa-

tients most often report their first symptoms and signs to the general practitioner. If a diagnosis is made early, the physician can give his patient the optimum chance for cure. In this respect the general practitioner becomes his own cancer-screening clinic. An improved cancer consciousness in all doctors is of primary importance in early diagnosis. This can mean a reduction in mortality and morbidity from cancer of the ear, nose, and throat. The general practitioner must realize that cancer of the ear, nose, and throat manifests itself in specific ways with many small significant signs and symptoms. Epistaxis, particularly in adults, persistent pain in the upper teeth, painless swelling of the cheek, and paresthesias of the cheek should lead the physician to suspect cancer of the nose or sinuses. Where nasal obstruction, postnasal bleeding, epistaxis, tinnitus, and hearing loss appear simultaneously, they should suggest cancer of the postnasal space. The dentist and the general practitioner have the best opportunity for early diagnosis of cancer of the tonsil. The best therapeutic results are obtained in cases of cancer of the larynx. This is one area in which diagnosis is possible in almost all cases. Surgery and roentgen-ray therapy have both given gratifying results in the treatment of chosen cases. Radical treatment in early cases of cancer of the ear gives an optimistic prognosis.

Miller, D.: The general practitioner and cancer of the ear, nose and throat. New England J. Med. 247:601-602, Oct. 16, 1952.

Gastric Cancer—Advances in Diagnosis

Many gastric cancers develop almost silently. No amount of public education or repeated examination will aid these cases. If gastric cancer is suspected clinically, patients should not receive symptomatic therapy until they have been studied roentgenographically. In order to arrive at an early diagnosis, the following steps are recommended: (1) seeing the patient early and following him carefully; (2) giving no symptomatic treatment; (3) performing a careful history and physical examination; (4) following examination by careful laboratory studies of blood count, urinalysis, serological studies, and usually gastric fractional analysis; (5) taking roentgenograms of the gastrointestinal tract; (6) making gastroscopic studies of the stomach; (7) taking biopsy of the gastric tissue; (8) studying cytologically the cellular elements of the stomach; (9) starting definitive medical or surgical treatment following a firm diagnosis; (10) if medical management fails after three weeks of careful observation, restudying the case thoroughly and again considering surgical exploration.

Recent advances in cytological methods and gastroscopic biopsy promise much for the future.

Shallenberger, P. L.: Advance in diagnosis of gastric disease. Pennsylvania M. J. 55:749-754, Aug., 1952.

Prostatic Cancer—Current Treatment

Most prostatic-cancer patients now live more comfortably and possibly longer than did those in the days before endocrine therapy. Early diagnosis of this disease is difficult, since the cancer causes few symptoms until late in its course. In cases in which rectal examination gives doubtful evidence, biopsy of the prostate must be performed. Radical surgery is the treatment of choice for occult prostatic cancer where the tumor is limited to the gland proper. When it has spread beyond the immediate boundaries of the gland, treatment is directed toward the relief of urinary symptoms and endocrine control of the tumor. The palliative treatment of inoperable prostatic cancer has been by methods based on androgen control. Castration combined with diethylstilbestrol is most effective in patients without metastases. Castration alone has been as effective as combined therapy in patients with metastases. There is at present no satisfactory

method for classifying cases of prostatic cancer according to their biological properties. Patients with advanced prostatic cancer inevitably suffer recurrences or reactivation of the tumor. Increase of the estrogen dose or changing to another estrogen may be of symptomatic benefit in such cases.

Brendler, H.: Evaluation of current treatment of prostatic cancer, J. Urol. 68:734-743, Oct., 1952.

Carcinoma of Colon and Rectum—Treatment

Treatment of carcinoma of the colon and rectum consists of eradication of the primary lesion or lesions and their present or potential metastases. It is advocated that the most radical procedures be applied to the younger, otherwise healthier, patient. Resection and primary anastomosis with or without complementary temporary colostomy proximal to the anastomosis are indicated in carcinoma of the colon from the ileocecal valve to the rectosigmoid. Resection will be limited in the presence of liver or inaccessible node metastases or a poor-risk patient. It will also be limited in solitary-cell pedunculated adenomas with early noninvasive malignant change, and in segmental involvement with multiple adenomas. A frank Grade-2, -3, or -4 carcinoma of the rectum, in the absence of distant metastases, usually requires a Miles type combined abdominoperineal resection with a permanent colostomy. Such a radical procedure is unjustified for adenomatous lesions with early malignant change. In a poor-risk patient the same lesion may be handled by simple-loop sigmoid colostomy and a posterior resection of the rectum by the Lockhart-Mummery technique.

Electrosnare and then thorough electrodesiccation of the base through the proctoscope should be sufficient treatment for the well-pedunculated tumor of the rectum without invasion of the stalk. Tumors with a stalk as well as some polypoid lesions may be handled by local resection and anastomosis or by proctosigmoidectomy after the method of Bacon. The Miles resection is widely accepted as the choice procedure in carcinoma of the rectosigmoid when cure, not palliation, is sought.

In the presence of a nonresectable lesion of the rectum, roentgen-ray and radium treatment may be justified. In palliative treatment, the choice will be the least extensive procedure that will help to relieve the patient of his chief complaint and does not demand a colostomy. The indiscriminate use of the colostomy in nonresectable, far-advanced cases that are not obstructed is not recommended, since the span of tolerable living is not increased by it.

McAdams, A. J.: Carcinoma of the colon and rectum; a discussion of various methods of treatment, Pennsylvania M. J. 55:743-745, Aug., 1952.

Prognosis in Carcinoma of Urinary Bladder

Carcinoma of the bladder is a chronic, recurrent disease and the urologist, the radiologist, and the chemotherapist must all co-operate in the treatment of any particular case. The expressions "surgical failure" and "radiation failure" should be discarded in the control of cancer and should be replaced by the idea of increased comfort and prolongation of life. Comparison of the cumulative survival rate by years in the authors' 347 cases with untreated cases revealed that treatment of cancer of the bladder appreciably prolonged life. The highest proportion of patients remained clinically free of disease if the cancer was treated by radium implantation rather than segmental resection. Comparison of the efficiency of the two types of treatment was based not on survivals but rather on the longest time interval that the patients were free from clinical evidence of disease. Radium implantation is recommended as the initial treatment in patients with grade 2 or more malignant, polypoid lesions and in submucosal nodular and sessile lesions. Treatment of carcinoma of the

bladder, whether initially considered definitive or palliative, prolongs life.

The 347 cases of carcinoma of the urinary bladder were classified in palliative and definitive groups based on gross pathology at time of operation, as follows:

	Radium Implant.	Segment. Resect.	Total
Definitive	107	103	210
Palliative	91	46	137
TOTAL	198	149	347

These cases were treated during the period 1925 through 1949.

Kligerman, M. M.; Robinson, J. N.; Fish, G. W., and David, I.: Segmental resection and radium implantation in the treatment of carcinoma of the urinary bladder. J. Urol. 68:706-713, Oct., 1952.

Nitrogen-Mustard Therapy

Thirty-six patients with Hodgkin's disease, lymphosarcoma, and chronic lymphatic leukemia were treated with HN2 in a dosage of 0.1 mg. HN2 per Kg. of body weight for seven days. To alleviate digestive disturbances, 25 mg. pyridoxine hydrochloride was given intramuscularly before each injection of HN2. Sixty-nine per cent of the patients showed diminution of one or more signs or symptoms. Anorexia, fatigue, and itching were more successfully relieved than were focal pain and lymph-node enlargement. Dyspnea when present, was relieved in 50 per cent of the patients, the improvement lasting for more than six months in half of those relieved. Fever associated with underlying disease responded to HN2 therapy in 90 per cent of the patients. Only three patients, however, all with Hodgkin's disease, remained free of fever for more than two months. Thirty-one per cent of the patients did not benefit from HN2 therapy. Approximately 50 per cent of the patients with low red-blood-cell and platelet counts showed an improvement in their red-cell or platelet counts with successful therapy. HN2 therapy was most effective in the alleviation of systemic complaints such as fever and pruritus, while radiotherapy is the treatment of choice for localized lesions causing focal signs.

Kieler, J.: Nitrogen mustard therapy in Hodgkin's disease, lympho-reticulosarcomatosis and lymphatic leukaemia. Acta Radiol. 36: 461-468, Dec., 1951.

Supervoltage Radiation in Breast Cancers

If radiation treatment is to increase survival rates in cancer of the breast still further, both the region to be treated routinely and the dose level at which to aim must be considered. It was found that, by using two million volt radiation and a rotational method of delivery, these requirements could largely be met. Any scheme of routine radiotherapy should include not only the axilla but also the chest wall and the mediastinum. The major advantage of the scanning technique is the ability to deliver a substantially uniform dose over a region extending from the axilla to the mediastinum bounded by the pleura on the inside and the subcutaneous tissues on the outside, using only two treatment fields. In supervoltage therapy both the tumor-volume dose and the total-body dose will vary considerably depending on the obesity of the patient and whether a mastectomy has been performed. To date ten patients have been treated by the methods described, All but one are alive from five to fifteen months after completion of treatment but there is one recurrence to date. Immediate skin reactions have not been severe. The authors believe 6000 r delivered in forty days to be a sterilizing quantity of radiation.

Hare, H. F.; Trump, J. G., and Webster, E. W.: Rotational scanning of breast malignancies with supervoltage radiation. Am. J. Roentgenol. 68: 435-447, Sept., 1952.

Breast Lesions in Well Women

Since the Cancer Prevention Center of Chicago, Inc., was opened in 1943, 17,000 women have been examined. The patients are well individuals who apply to the Clinic for a complete examination. Of 7767 patients examined

in a two-year period, a definite mass was found in 129. Fifty-four of these had biopsies and of these ten, or 18.5 per cent, were found to be carcinomas. Thirty-seven, or 68 per cent, of the masses were benign.

It is believed that the figures presented from the Chicago Clinic represent the incidence of breast pathology in the apparently well woman. Approximately 5 per cent of the apparently normal female population has clinically demonstrable breast lesions. In order to detect early carcinoma, routine breast examination and biopsy of suspicious lesions are indicated. It is the duty of every physician who sees a breast lesion to do a pelvic examination, since there can be no doubt that there is some specific correlation between breast and pelvic disorders.

Examination of the breast consists of inspection and careful palpation of the breasts and the supraclavicular and axillary areas. If abnormalities are found, the patient is referred to her own physician for diagnosis and treatment.

Phillips, M. A., and Miller, J.: Incidence of breast pathology in well women. Illinois M. J. 102:176-179, Sept., 1952.


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POUR

LE DOCTORAT EN MÉDECINE

Par J. DUZAN,

DU CANCER
CHEZ LES ENFANTS

PARIS

1876

First extended work devoted solely to cancer in children.

at a glance . . .

one-minute abstracts of the current literature on cancer . . .

Wilms's Tumor in Childhood

Wilms's tumor constitutes about 20 per cent of all malignant tumors of childhood, is rapidly growing, and is usually silent until it induces symptoms by its mechanical effects. It may arise from any portion of the kidney and is probably best considered as an embryonal neoplasm of indefinite origin. The most common symptom and physical finding is an abdominal mass that has shown a progressive and painless enlargement. About 80 per cent of the cases occur before the age of 8 years. Hematuria is usually regarded as a late symptom and its presence carries a poor prognosis. Pyelography is an essential diagnostic aid in this disease. Prognosis is usually poor. Recurrences usually appear in six to eighteen months, although they have been reported as late as four years following operation. However, if the patient survives two years without evidence of recurrence there is a good probability of a cure. The histology, cell type, or size of the tumor seem to have no relation to its curability, but age seems to have a very definite effect, it being clearly evident that the younger the child the better the outlook for a cure.

There is a difference of opinion as to whether radiotherapy should precede surgery, but there seems to be a fairly general agreement that neither surgery alone nor irradiation alone is sufficient and that a combination of the two procedures is the treatment of choice. Fairly extensive irradiation of the metastases is indicated. Irradiation should not be withheld in the inoperable case no matter how dark the outlook may seem, since remarkable cures have been reported in such cases. Eight proved cases of Wilms's tumor are presented.

Benzing, W., Jr.: Wilms' tumor of infancy and childhood. Radiology 58:674-687; disc. 711-713, May, 1952.

Papilloma of the Larynx in Children

Papillomas are the most common tumors of the larynx in children and are cancerous in their rapidity of growth, their tendency to recur, their ominous sequelae, and their fatal termination in many cases. Symptoms are similar to those usually present in all neoplastic conditions of the larynx. Laryngeal papillomas occur most frequently between the ages of 15 months and 4 years but may occur at any age. Diagnosis can only be made by a careful

history and direct laryngoscopy and must be made early if treatment is to be effective. Biopsy should be performed in all cases. Emphasis must be placed on conservative treatment because the lesion is histopathologically benign and self-limiting in the majority of cases. The method of choice in the treatment of laryngeal papillomas in children is repeated endolaryngeal excision using biting forceps flush with the adjacent mucosal surface.

Gorrell, D. S.: Laryngeal papillomata in children. Canad. M. A. J. 67:425-427, Nov., 1952.

Skin Tumors in Children

The great attention focussed on cancer in children is due largely to the fact that the tumors are often highly malignant and rapidly fatal. The death rate from cancer in the age group of 1-to-4 years is 40 per cent higher than in the 5-to-9-year age group, and 80 per cent higher than in the 9-to-14 group. Tumors considered specific for childhood occur mainly in the first few years of life and begin to decline sharply in incidence in the second period. In the third period the childhood varieties of neoplasms occur only very rarely. The embryonal, sarcomatous, or mixed tumors are characteristic of infancy, the best known of these being Wilms's tumor of the kidney, the various teratomas, the adrenal and retinal neuroblastomas, and the embryonal rhabdomyosarcomas. Since these embryonal tumors develop on the basis of dysontogenesis, often within the span of intrauterine life, they are clearly set apart from the ordinary cancers of adult life that probably arise only after long exposure to various carcinogenic agents yet to be defined.

Benign tumors are encountered far more often and require keener judgment with regard to histological diagnosis and treatment than do the relatively rare malignant tumors. At Memorial Hospital approximately twenty-five benign tumors are seen to every malignant one in children, most of the benign tumors being cutaneous. There is often great disparity between the histological appearance and the subsequent clinical course in certain skin tumors of childhood. The clinical course of histiocytoses cannot be determined by the histological appearance of cutaneous lesions. The benign juvenile melanoma, which constitutes a very small segment of childhood nevi, may frequently be mistaken for malignant melanoma. "Juvenile" melanomas should be removed by simple surgical excision. Common lesions such as hemangiomas are generally better treated by methods other than irradiation. Since there may be confusion clinically concerning the exact nature of certain cutaneous nodules, biopsy and histological diagnosis are essential before therapy is begun.

Spitz, S.: Cutaneous tumors of childhood; disparity between clinical behavior and histologic appearance. J. Am. M. Women's A. 6: 209-219, June, 1951.

Cancer in Children

Cancer is now a major cause of mortality in early life, causing 10 per cent of the deaths from diseases during childhood. In 1949 a Tumor Diagnostic Service for Children was established by the St. Christopher's Hospital for Children in conjunction with the State Department of Health. To date more than 150 specimens from suspected neoplasms of infants and children have been submitted to the Tumor Diagnostic Service for Children. Sarcomas comprise the majority of malignant growths in early life.

There are certain important differences between neoplasms of childhood and those of adults. The clinical pattern is often quite different, cancer in early life being for the most part a rapidly progressive, relatively acute disease suggesting an acute infectious process rather than a cancer. Moreover, there are certain sites of predilection for cancers in early life. Leukemia, neuroblastoma, Wilms's tumor, intracranial tumors, and bone cancers are

all important groups of neoplasms in childhood. Certain generalizations are stated concerning both diagnosis and therapy of cancer in infants and children: (1) every solid mass should be regarded as a malignant tumor until its exact nature is determined by histological examination of the removed tumor; (2) undue palpation of the tumor should be avoided; (3) the tumor should be removed as soon as possible, usually within twenty-four to forty-eight hours.

Although prognosis is usually very grave, recent advances in diagnosis and therapy have resulted in encouraging rates of cure in a number of cancers observed in infancy and childhood. Leukemia continues to have a hopeless prognosis but remissions may be induced in a significant number of patients. A table gives a résumé of common malignant neoplasms in early life with signs and symptoms, primary site, diagnosis, treatment, and prognosis.

Arey, J. B.: Cancer in infancy and childhood. Pennsylvania M. J. 55:553-557, June, 1952.

Bone Tumors in Children

This is an analytic study of 412 bone tumors in children from infancy to 14 years of age seen at the Children's Mercy Hospital (Kansas City, Missouri) and in private practice of radiology. Three new bone lesions are included, namely, osteoid osteoma, fibrous dysplasia, and eosinophilic granuloma. To be considered in the differential diagnosis of osteoid osteoma are chronic osteomyelitis or sclerosing osteomyelitis and atypical osteosarcoma and endothelioma of the bone. Osteoid osteoma may be distinguished from malignant bone disease by the well-localized topographical pattern and absence of true bone destruction characteristic of osteoid osteoma. Roentgenographically fibrous dysplasia may be confused with von Recklinghausen's disease, enchondroma, or simple bone cyst. In its monostotic form it may simulate a chondroma or even a giant-cell tumor. Malignant changes have been reported in the regions of fibrous dysplasia. Cartilaginous tumors, the Hand-Schüller-Christian syndrome, multiple myeloma, and angioendothelioma must be considered in differential diagnosis of eosinophilic granuloma.

Walker, J. W.: Experiences with benign bone tumors in pediatric practice. Radiology 58:662-673; disc. 711-713, May, 1952.

Congenital Leukemia

Leukemia occurs in the first five years of life much more frequently than in other five-year periods and a very large proportion of the cases are of the acute variety. An 8-year-old female infant presented a typical picture of so-called "congenital leukemia." She was admitted to the hospital with a diagnosis of pneumonia and anemia. Physical examination showed a very pale but well-developed and well-nourished child with rapid wheezy respirations and a temperature of 104° F. The mucous membranes of the mouth showed several irregular areas of dark-red discoloration with no evidence of ulceration. The arms and the left thigh presented several areas of ecchymotic discoloration. The abdomen was round and distended. Red cells numbered 3,320,000; hemoglobin was 62 per cent; white cells numbered 180,000, a large number being immature. There were 2 per cent normoblasts. Death occurred twelve hours after admission. The baby had suffered from thrush when 1 week of age, which may have been a manifestation of leukemia. "Black and blue" areas on the skin of the arms had been noticed some time before admission. These also may have been a manifestation of leukemia very soon after birth. At autopsy, the organs were already infiltrated with a very large number of tumor cells. The kidneys and especially the pancreas were disproportionately increased in size. It is believed that the present case may well be added to the twenty or more recorded cases of "congenital" leukemia.

Beliveau, R. A.: Leukemia, with special emphasis on "leukemia in infants." J. Maine M. A. 43: 65-67, March, 1952.

Upper Gastrointestinal Tract Lesions in Children

New growths of the stomach are rare in children but they are frequently the source of obscure bleeding from the intestinal tract. The majority of new growths of the stomach are benign tumors and polyps and have been best demonstrated by means of compression spot-film and radiography. Primary lymphosarcoma of the bowel, although relatively rare in children, is the most common type of sarcoma of the intestinal tract and is located most frequently in the terminal ileum. Early pain is frequently present and there is usually an associated loss of weight and strength and secondary anemia. An abdominal mass may be palpated. A segment of dilated small bowel may show up on a scout film of the abdomen owing to submucosal nerve-plexus involvement rather than mechanical obstruction. An irregular, rigid, somewhat dilated segment of bowel is characteristic, the opaque medium being retained over a period of several hours as a result of the localized lymphosarcomatous infiltration.

Lockard, V. M.: Lesions of the upper gastrointestinal tract in infants and children. Radiology 58: 696-704; disc. 711-713, May, 1952.

Nursing Care of the Leukemic Child

A basic incentive for the nursing care of each leukemic child is the hope that research in leukemia will unearth a cure for this at present incurable cancer of the blood. When first admitted to the hospital the child is given time to get acquainted with his surroundings and the nurses. A strong effort is made to prepare him for each laboratory test. Every effort is made to gain the confidence of the mothers. Children who are feeling well are encouraged to lead a normal life. In leukemia the battle is to keep the confidence of child and parents. The "in and out" patient requires special psychological treatment and when the child is permanently re-admitted as an acutely ill patient, both the physical and psychological aspects of nursing care are intensified. The nurse tries to cater to the leukemic child's appetite. Maintaining cleanliness becomes a problem as the disease progresses because of weakness, pain in the joints, and increasing frequency of bleeding. An oxygen tent may be ordered in the final stage if it affords relief. The nurse tries to keep the child as happy as possible with entertainment — birthday parties with cake and ice cream, balloons and presents, radio and television, and amusing stories.

Scott, R. B.: Nursing care of the child with leukemia. Nursing World 126:16-17, Aug., 1952.

Treatment of Leukemia

In the treatment of leukemia the complete care of the patient, mentally and physically, is of the greatest importance. Specific and supportive measures available today give the patient with leukemia a course of relative comfort. They give the patient with chronic leukemia years of active, comfortable and economically efficient life. The life span of acute leukemic patients varies from a few days or weeks to several months. There may be spontaneous remissions or remissions may be induced by therapeutic agents such as pituitary and adrenocortical hormones and folic acid antagonists. ACTH and cortisone may induce rapid and striking hematological remission in 40 to 60 per cent of cases. Aminopterin will produce clinical and hematological improvement in from 40 to 60 per cent of cases of acute leukemia in children and from 10 to 15 per cent of such cases in adults. ACTH is the drug of choice in acute leukemia in both children and adults, with folic acid antagonists as alternates. Present methods of therapy have prolonged the period of gainful life of the chronic leukemic patient. Irradiation is deemed to be the best available form of therapy for chronic myelocytic leukemia. Radioactive phosphorus has the advantage of ease and simplicity of administration (by mouth) but it is available only at institutions specifically

equipped to handle radioactive materials. Chemical agents used in treatment of chronic myelocytic leukemia include Fowler's solution, urethane, nitrogen mustard, and triethylenemelamine (TEM). Chronic lymphocytic leukemia is best controlled by roentgen rays or P^{32} administration. Urethane may be effective in selected cases. Nitrogen mustard is somewhat more effective and the disease has also been controlled by TEM.

Rambach, W. A., and Alt, H. L.: Treatment of leukemia. GP 5:67-73, March, 1952.

Triethylenemelamine in Cancer Treatment

Triethylenemelamine (TEM) has proved to be especially useful in the treatment of the chronic proliferative diseases arising from lymphatic tissue. Localized Hodgkin's disease and localized lymphomatous tumors are best treated with roentgen-ray radiation. TEM is a promising agent in managing diffuse nonlocalized disease and may compare favorably with whole-body irradiation and P^{32} in this respect. When the bone marrow is involved, as in chronic lymphocytic leukemia, the beneficial effect of TEM administration surpasses that of any other agent. In atypical and subleukemic granulocytic leukemia and in multiple myeloma, the results with TEM have not been promising. TEM therapy has been of little value in acute leukemia, rapidly progressing malignant lymphomas, and in most nonhemopoietic tumors. The palliative effects in nasopharyngeal lymphoepithelioma and in ovarian papillary cystadenocarcinoma with mestastases have been worth while. The critical problem in TEM therapy is the administration of therapeutically adequate amounts while avoiding the serious hazards of overdoses. The correct dose must be determined empirically for each patient. TEM appears to be an agent well suited for sustained therapy without producing cumulative damage to normal tissues. It may be used advantageously in conjunction with local roentgen-ray therapy and in cases in which whole-body irradiation or P^{32} has been used. Triethylenemelamine is an important addition to the chemotherapeutic agents useful in the treatment of cancer.

Rundles, R. W., and Barton, W. B.: Triethylene melamine in the treatment of neoplastic disease. Blood 7: 483-507, May, 1952.

Brain Tumors in Children

Vomiting, unsteadiness and a positive Macewen's sign comprise the diagnostic triad for an intracranial tumor in a child. Severe occipital headache may also be present. Two thirds of the tumors that give clinical signs before puberty are below the tentorium. The average survival time in medulloblastomas varies from six months to five years. They are most common in males from 3 to 6 years of age. Treatment consists of cerebellar decompression and postoperative roentgen-ray therapy. Most tumors of the pons and medulla are highly malignant, infiltrating gliomas, resistant to all forms of treatment and resulting in death within a few months. Prognosis is worse in the younger age group, since medulloblastoma is more common in children of this age and they are poorer surgical risks. In the present group of thirty-four cases of brain tumor the children ranged in age from 11 months to 15 years, nineteen being in the age group from 11 months to 6 years. Twenty-five of the children were dead or unimproved at the end of a year and nine were living and improved for more than one year. Roentgen-ray therapy was administered to ten of the patients, of whom seven died and three were improved, the tumors in these three cases being a fourth ventricle medulloblastoma in a 10-year-old, an unclassified third ventricle tumor in a 13-year-old, and a cerebral glioblastoma multiforme with extensive calcification in a 15-year-old child.

Smith, A. B.: Brain tumors in children. Radiology 58: 688-695; disc. 711-713, May, 1952.

Intracranial Lesions in Childhood

Prognosis in expanding intracranial lesions remains particularly poor during infancy and childhood, although it is improving. Medulloblastomas are always malignant, the average length of life from time of diagnosis for children with this tumor being sixteen to eighteen months. Glioblastoma multiforme is just as malignant. Astrocytomas can sometimes be successfully removed and without residual damage. The expanding intracranial lesions are classified into eleven categories. It is fallacious, even dangerous, to regard all expanding intracranial lesions in childhood as gliomas or other limited types of tumor. Infratentorial lesions, especially of the glioma group, are more common than supratentorial lesions. Age at onset was of no value in predicting the type of lesion to be expected in any given patient. Choked disc was the most frequently observed physical finding. The patients presented multiple rather than single symptoms, vomiting and headache being most often recorded. Widening of sutures, intracranial calcification, and distortion or erosion of the calvarium are roentgen-ray findings that aid the diagnosis and may even localize the tumor. Improved techniques have made skull roentgenograms and ventriculography increasingly helpful in the diagnosis of these lesions in children. Ventriculography proved to be less hazardous than exploratory craniotomy. During the twenty-two-year period ending July 1, 1951, 104 children with expanding intracranial lesions have been admitted to the Denver Children's Hospital, in whom histological proof was obtained in ninety. All patients were less than 15 years of age.

Palmer, H. D., and Murphy, E. S.: Expanding intracranial lesions in childhood. J. A. M. A. 149: 220-227, May 17, 1952.

Radiological Diagnosis of Respiratory Lesions in Children

The first problem is to obtain adequate roentgenograms from the technical standpoint. When unquestionably pathological shadows are seen, in order to justify any interpretation at all, the radiologist must put aside etiological entities and go back to the basic pathological and physiological changes he can recognize, including infiltration, consolidation, cavitation, vascular congestion, emphysema, and atelectasis. Primary lung neoplasms are rare in children except for the lymphoma group with mediastinal involvement and secondary effects on the pulmonary system. The metastatic lesions are by far the most prominent of the lung neoplasms, the majority being metastases from Wilms's tumor of the kidney, neuroblastoma, and the osteogenic-sarcoma group. Usually multiple, they may be solitary and range in size from discrete small lesions to masses involving an entire lobe or even an entire lung. Neoplasm may be differentiated roentgenographically from a pneumonic process by the absence of any associated obstructive atelectasis or emphysema.

Chapman, S. B.: Radiologic diagnosis of respiratory lesions in children. Radiology 58: 705-710; disc. 711-713, May, 1952.

"It is of great interest to note that malignant disease is not mentioned in any way in the [Shakespeare] plays nor, as far as I can find out, in the literature of the period. It is unlikely that such a serious and, as it were from the poetic angle, colorful disease would escape the poet's observant eye. I think it is very probable that malignant disease was much less common in those days; a factor, of course, was the very much shorter expectation of life."

Rose, B. T.: Medicine in the days and plays of Shakespeare. Birmingham M. Rev. 17:234-250, 1952.

The Diagnosis of Certain Tumors of Childhood

Harold W. Dargeon, M.D.

The methods used in the diagnosis of cancers of children are similar in principle to those employed in the diagnosis of any disease of childhood. They consist of the history and physical examination—a major part of the diagnostic approach—standard laboratory diagnostic procedures such as blood counts and urine analysis; special laboratory procedures such as marrow examination, cytological (Papanicolaou) studies, roentgenography, and biopsy. The fallacy of constant reliance on a single diagnostic approach for any clinical problem is evident in the instance of childhood neoplasms. In many cases, only one or several procedures are necessary to reach a diagnosis. In others all methods will be found inconclusive. Complete dependence upon even histological diagnosis places a responsibility on the pathologist that he cannot accept in all cases.

The first step in the endeavor to establish the diagnosis of any disease is to suspect its presence. The infrequency with which neoplastic disease occurs in pediatric practice accounts partly for the fact that there is a delay—sometimes measurable in months—between the onset of symptoms and the establishment of the diagnosis. That improved and more prompt diagnosis offers promise of much greater salvage of children is testified to by the increasing numbers of five-year survivors of such cancers as medulloblastoma, lymphosarcoma, neuroblastoma, Wilms's tumors, some of which are still generally considered to have a universally hopeless prognosis. Earlier diagnosis can be made if several considerations are followed:

1. Differential Diagnosis. Neoplastic disease should be included in the differential diagnosis of the acute and subacute as well as of the chronic illnesses of childhood. The fulminating symptoms associated with some intracranial, intrathoracic, and intra-abdominal tumors can be as acute and dramatic as those that may occur in any surgical emergency. It need hardly be stated that in ANY subacute or chronic illness, cancer is one of several possibilities to be investigated.

2. The Atypical Symptom Complex. This simply means that in the absence of the ordinary corroborative signs—or a departure from the usual clinical course of the disease assumed to be present—neoplasm, among other unusual conditions, should be considered. This may be illustrated by one of the commonest of all childhood conditions—the traumatic swellings that all runabout children sustain almost daily. These usually subside within hours or days and do not cause pain after a few days or even less. A tumor of the soft parts, however, deviates from this usual course in several ways: (1) it makes its appearance generally in the absence of trauma; (2) it is usually painless initially; (3) it may cause discomfort or actual pain AS TIME ELAPSES; (4) it does not subside; (5) it usually grows.

The histories of most children with different types of cancer duplicate this general clinical course frequently. There is first a fairly evident cause for the child's illness but as time passes the disease behaves peculiarly and does not fit the pattern of the condition initially considered, either as to clinical signs or as to therapeutic response.

Anatomical Sites of Greatest Frequency

It will be recalled that most of the common tumors of adult life are observed so seldom in the child as to be considered medical rarities. The tumors of greatest frequency are those involving the following sites (Fig. 1): (1) intracranial region, (2) eye, (3) soft somatic areas, (4) bones, (5) kidney, (6) marrow and other hematopoietic areas.

Some of the more common symptoms that occur in tumors of these sites are as follows:

1. *Intracranial Region.* Although many intracranial areas may be the site of the primary tumor, the posterior fossa, the hypophysis, and—to a less frequent degree—the cortex are the areas of greatest occurrence.

POSTERIOR FOSSA. Cerebellar symptoms (ataxia, muscle weakness, etc.) and often intracranial hypertension: vomiting (unrelated to diet or time of meals), headaches, expanding skull occur.

HYPOPHYSIS: somatic changes, physical and intellectual precocity, intracranial hypertension, visual impairment occur.

CORTEX: motor or sensory defects, psychic alterations ensue.

2. *Eye.* Visual defects, change in pupillary reaction and size, and change in color of pupillary reflex to gray, green, white occur.

3. *Soft Somatic Areas.* Swellings of various sizes, shapes, and consistencies are found. If cutaneous, the skin color may be altered.

4. *Bones.* Pain, discomfort, muscular disabilities from mild to severe degrees, and night cries occur.

5. *Kidney.* Abdominal or flank mass, rarely hematuria, fever, or hypertension is found.

6. *Marrow and Other Hematopoietic Structures.* Pallor, asthenia, fever, myalgias, tumefactions in the nasopharynx, mediastinum, and abdomen, and adenopathy that may at times be rapid in development ensue.

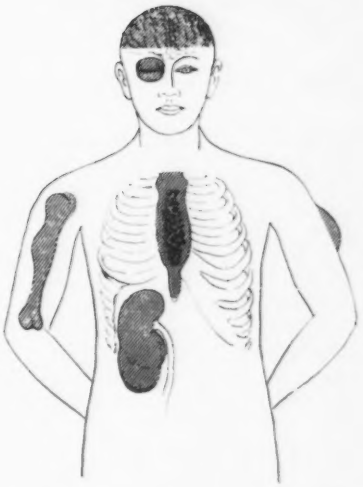

Figure 1. The sites of greatest frequency of children's tumors.

For refinements in diagnosis many well-known laboratory tests and roentgenographic procedures are readily available to any practicing physician. However, a clue to the cause of the child's illness should be found and a general, if not histologically specific, diagnosis of most neoplasms in childhood obtained by reviewing these considerations in any pediatric diagnostic problem. The internist may require the laryngoscopic mirror, the vaginal speculum, the proctoscope, and other equipment to perform a satisfactory examination on the adult. The practitioner who treats children need only utilize the elementary methods of physical diagnosis—observation, palpation, percussion, auscultation—to diagnose provisionally the presence of the great majority of all tumors of children.

Reference

Dargeon, H. W.: Cancer in children from birth to fourteen years of age. J. A. M. A. 136: 459-468, 1948.

Tumors of the Lymphoma Group in Children with Special Reference to the Treatment of Acute Leukemia

Sidney Farber, M.D.

Tumors of the lymphoma group, including acute leukemia, comprise one of the largest groups of tumors in infants and children. Acute leukemia, itself, which occurs much more frequently in early life than in the adult, is the most common malignant tumor in children in our experience, ranking in frequency far ahead of the neuroblastoma and the Wilms's embryoma of the kidney. Chronic leukemia is rare in early life, as are Hodgkin's disease and the several forms of lymphosarcoma. A common form of lymphoma is that which runs a rapid course over a period of weeks to months and terminates in an acute leukemia.

This discussion will be concerned primarily with acute leukemia; only brief reference will be made to the treatment of other members of the lymphoma series. It is based on our experience with the use of chemical agents and hormones as part of the total care given to more than four hundred children with acute leukemia in the past six years.

Acute Leukemia in Infancy and Childhood

Acute leukemia runs an invariably fatal course, within a few weeks to several months after onset when no special treament is employed—with rare instances of survival for more than a year. Spontaneous remissions, lasting an average of nine weeks, occur in from 1 to 10 per cent of children with acute leukemia. These are related to immediately preceding severe infections such as cellulitis or bacteremia. The chief clinical and pathological findings are explained by the almost complete replacement of the bone marrow by tumor cells usually of the stem-cell type, and the infiltration, either slight or massive, of most the organs and tissues of the body with greatest effect upon the spleen, the liver, lymph nodes, bones, and kidneys. The chief causes of death are HEMORRHAGE, which may be massive, in the gastrointestinal or urinary tracts, the skin, the lungs, and the brain; INFECTION, characterized usually by bacteremia produced by the common pathogenic organisms, many of which are resistant to antimicrobial agents, and some of which are ordinarily not regarded as highly virulent; and last in frequency, TUMOR INFILTRATION, actually responsible for death, as in the case of involvement of the heart, the mediastinal lymph nodes, and the kidneys.

Presenting signs and symptoms in acute leukemia in children include those referable to anemia, such as pallor, lassitude, weakness, anorexia, and irritability; those concerned with hemorrhage, either petechial, ecchymotic, or massive as from the nose or gastrointestinal and urinary tracts, and those secondary to the presence of tumor masses or infiltration of organs leading

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NOTE: This paper is based upon studies carried out by a group of doctors for the past six years. Senior members at this time include Dr. Ruth Appleton, Dr. James P. King, and Dr. Virginia Downing who have helped to prepare the material on which this manuscript is based.

to enlargement of the liver, spleen, or lymph nodes. Such involvement of the mediastinal lymph nodes, for example, may explain cough and dyspnea. Pain caused by the infiltration of bones and joints or infections of the respiratory tract and the skin indicative of increased susceptibility to infection may dominate the clinical picture.

The clinical diagnosis is confirmed by study of the peripheral blood and bone marrow. The total leukocyte count may be very high (50,000 to 500,000 or more) or more commonly, less than 6000. The platelet level may be lower than 50,000. In most instances on first admission the platelet level may be as high as 100,000 to 150,000. The erythrocyte and hemoglobin levels reflect the replacement of the marrow of leukemic cells. The marrow in relapse contains tumor cells in amounts usually between 80 to 99 per cent. The findings of more than 7 per cent of "blasts" or stem cells in the marrow is consistent with the diagnosis of acute leukemia, which in children is usually of the stem-cell variety. Rarely acute monocytic, lymphocytic, or myelocytic types may be recognized.

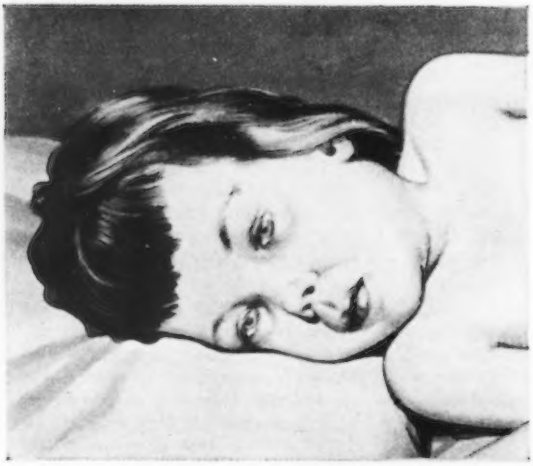
Prior to 1948 the usual treatment for acute leukemia in most clinics of the world consisted in verification of the diagnosis, transfusion, and sending the patient home with the expectation that the exitus would occur within a few weeks to a few months. The production of remissions in acute leukemia by the use of folic acid antagonists and later ACTH and cortisone justifies the conception that we have advocated of the use of total care in the treatment of the child with acute leukemia. Such care includes the use of all medical knowledge for the relief of pain, the prolongation of what has been proved to be good life in so many instances, and the giving of happiness to the child and his family. Antimicrobial agents, blood transfusions, and irradiation are used in addition to any new form of treatment directed against the leukemic process itself. Implicit in the adoption of such a policy is the decision to treat every child with acute leukemia with such total measures and to continue such treatment as long as the patient is alive. Justification for such a policy is found not only in this interpretation of the full duties of the physician but also in the fact that in no field of cancer research today is there so much progress as in that concerned with the search for new chemical or other agents that may affect the treatment of acute leukemia.

Treatment must be directed therefore toward prevention or cure of severe infection by the use of antimicrobial agents, against hemorrhage by the use of blood transfusions as required until the bone marrow is returned to a more normal state, and finally toward removal of the leukemic cells in the marrow and the organs and tissues of the body by more specific measures. As part of total care, two special forms of treatment of acute leukemia are available today.

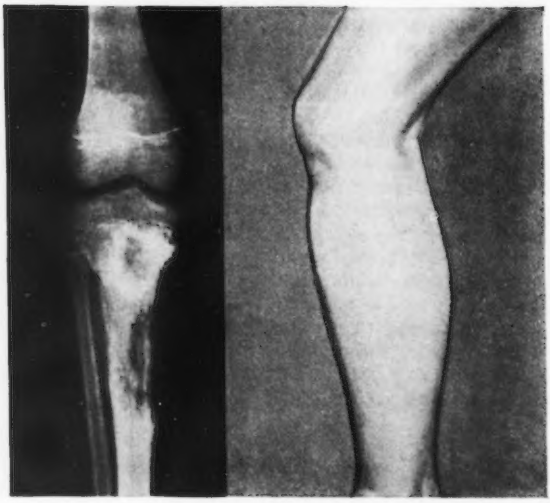
Aminopterin and Other Folic Acid Antagonists

Aminopterin (4-aminopteroylglutamic acid) may be taken as representative of the group of folic acid antagonists with closely related chemical structure. The dose is adapted empirically to the age and weight of the patient and is dependent upon the response of the patient and the development of early signs of toxicity. In general, in the age group from birth to 2 years, a total dose of 0.25 to 0.5 mg. is given; from 2 years to 5 years, 0.5 to 0.75 mg.; and over 5 years of age from 0.75 to 1.0 mg. The dose of amethopterin (4-amino-10-methylpteroylglutamic acid) is approximately five times that of aminopterin. Children tolerate larger relative and absolute doses than do adults. Usually aminopterin is administered once a day, six times a week, in most instances by mouth, although intravenous and intramuscular routes may be employed. Therapy is continuous except when manifestations of toxicity are observed. The earliest

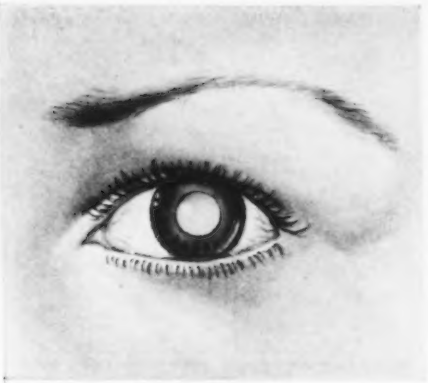
Malignant Tumors of Childhood



Leukemia—Pallor, anemia, increasing fatigue and listlessness. Enlarged lymph nodes, spleen, and liver. Hemorrhagic phenomena—petechiae, joint pains, frank hemorrhage. Lymph-node enlargement. Differential leukocyte counts of blood and bone marrow. Antifolic compounds, ACTH, and cortisone for amelioration. Fatal.

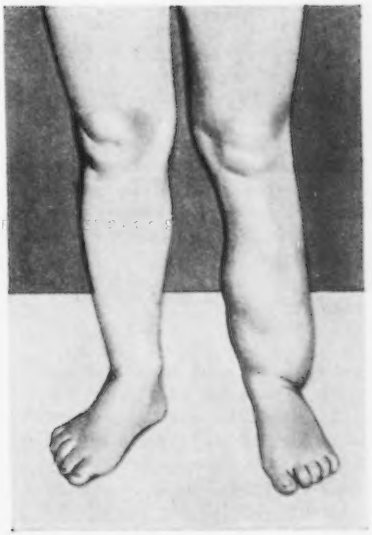


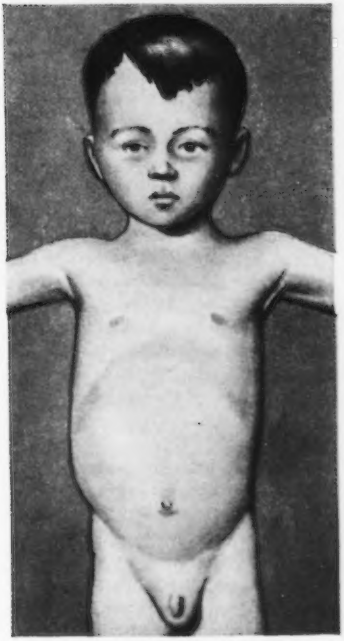
Osteogenic Sarcoma and Ewing's Sarcoma—Painful joint or bone area, voluntary limitation of motion. Often associated with gradual enlargement. Immediate radiographic study. Biopsy. Early amputation, if disease is in long bones.



Retinoblastoma—Squint, inability to co-ordinate with normal eye. Amaurosis. Normally black pupil changes to gray in strong light. Eye-ground examination reveals mass. Enucleation and/or roentgen-ray therapy. Bimonthly examination of other eye. Examine siblings and advise parents regarding hereditary considerations.

Somatic Sarcomas—Masses in many subcutaneous sites. Similarity to each other precludes absolute differentiation clinically. Biopsy by aspiration, punch, or incision. Wide surgical removal; rarely radiosensitive.





Wilms's Tumor (Embryoma) — Increase in girth, abdominal mass. At times pain in loin or abdomen, hematuria, frequency. Highly sensitive to irradiation, but surgical removal is the method of choice.

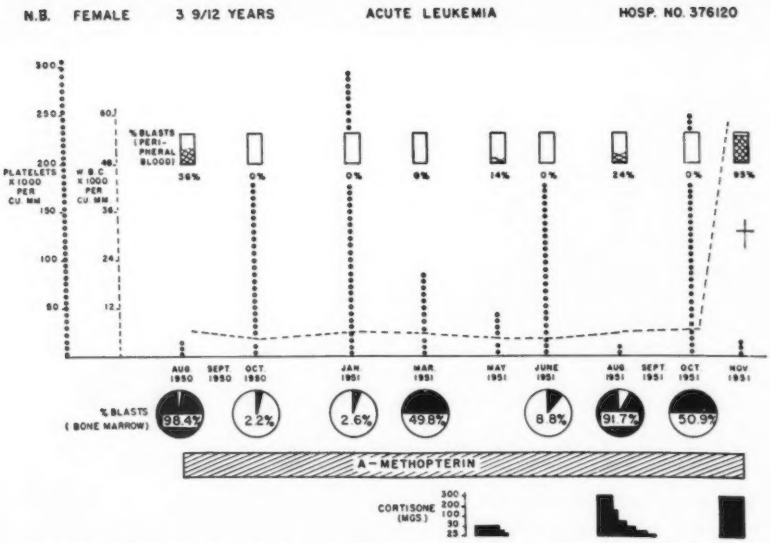


Figure 1. This illustrates an average experience in the treatment of a child with acute leukemia who survived for thirteen months after the onset. The vertical dotted lines represent the level of platelets, which serves as a good indicator of the state of relapse or remission. One remission was produced by the use of amethopterin; when cortisone was added at the time of relapse a second remission was produced. Note the return of blasts in the peripheral blood in times of relapse and their disappearance from the peripheral blood in times of remission. Death occurred because of bacteremia.

and most reliable signs of toxicity are stomatitis, abdominal pain, and diarrhea. If stomatitis occurs, therapy should be stopped until this evidence of toxicity subsides. Aminopterin may then be given again, usually in a somewhat smaller dose. If the amount of aminopterin is chosen to meet the needs of the individual patient under careful observation, toxicity of severe degree may be avoided completely. In our experience 65 per cent of the children developing remissions never developed signs of toxicity. In the majority of the remainder toxic manifestations were usually mild, requiring for their treatment merely the discontinuance of therapy for a few days.

A white count of less than 4000 and platelet counts of less than 50,000 should not be regarded as contraindications to the use of aminopterin, since the explanation for such bone-marrow depression lies in the infiltration of the marrow by leukemic cells. In twenty-five of thirty-two children with acute leukemia, in whom white counts and platelet counts of such low level were found, marked improvement was produced by the use of aminopterin.

ACTH and Cortisone

Both ACTH and cortisone are of value in the treatment of acute leukemia. Cortisone is employed more frequently because it may be given orally, a matter of importance in children, particularly those in whom hemorrhage is a problem. After relapse, or failure to respond to cortisone, remissions have

been produced by the use of ACTH. Cortisone given either orally or intramuscularly is employed in the following doses:

From 6 mo. to 2 yr.	60-100 mg. per day
2 to 5 yr.	75-150 mg. per day
5 to 10 yr.	100-150 mg. per day
10 to 15 yr.	100-200 mg. per day

These amounts are given in three or four divided doses for a period of ten to fourteen days; during the first seven days of this period the full dose is given with gradual lowering of the dose to the point of discontinuation. A second or third course varying from two to six weeks in duration may be given. ACTH may be given both intramuscularly and intravenously. The aqueous preparation injected intramuscularly is given in three or four divided doses daily. When the proper dose level has been achieved it is possible to change to Acthar-gel (Armour), which can be given intramuscularly once daily. The dose schedule for ACTH given intramuscularly is as follows:

From 6 mo. to 2 yr.	20-40 mg. daily
2 to 5 yr.	30-50 mg. daily
5 to 10 yr.	40-60 mg. daily
10 to 15 yr.	60-100 mg. daily

Under certain conditions ACTH may be given intravenously in doses 1/8th to 1/4th of that used intramuscularly in a slow intravenous drip over a twelve-hour period.

Choice of Treatment

In most instances aminopterin or amethopterin is the drug of choice, as soon as the diagnosis of acute leukemia is made. These chemical compounds are easier to give than the hormones, and the dose may be controlled with the aid of routine hematological studies with particular emphasis on the level of the white blood cells and the platelets. The remissions so induced are of longer duration than those following the use of the steroid hormones. It should be emphasized that at least three weeks of continuous therapy usually are required before hematological improvement occurs. Clinical improvement of marked degree may be apparent many days before there is hematological evidence of remission. Eventually resistance to the drug employed, whether aminopterin, or cortisone, or ACTH, must be expected in every child who does respond initially. Further improvement may be expected in 65 per cent of the children treated with cortisone after resistance to aminopterin has developed.

Certain exceptions in the choice of specific therapy should be mentioned. Children who are severely ill on admission are given combined aminopterin and cortisone therapy. Those with large lymphosarcomatous masses in the mediastinum or kidney regions respond more readily to ACTH or cortisone than to aminopterin. Irradiation in small amounts is also employed to produce rapid shrinkage when serious symptoms are produced by large masses in the mediastinum or in the kidney region. Adolescents respond best to a combination of ACTH or cortisone and aminopterin.

Results of Treatment of Acute Leukemia

Approximately two thirds of children with acute leukemia show marked temporary improvement on aminopterin therapy. There have been no cures. This experience has been verified in many clinics in this country and abroad. Approximately the same percentage respond to ACTH or cortisone, or when both the chemical and the hormone are employed. Of 100 children treated initially with aminopterin, or other related compounds, and later by ACTH or cortisone, 86 per cent showed marked improvement and an important increase in survival time. Improvement may be defined in terms of a return to a state indistinguishable from normal clinically, or both clinically and hematologically. Survival time in those who respond is increased by several months over that in children with acute leukemia who are not

treated by special means. Fifty per cent of our patients have survived more than eleven months. The sooner the treatment is begun after the diagnosis is made the better the chance for a long survival. Ten per cent of patients treated with aminopterin and the hormones have survived almost nineteen months. One child is still alive and in excellent health with the remission lasting more than forty-three months while under continuous folic acid–antagonist treatment. During this entire time he has grown and developed normally.

Lymphosarcoma, Hodgkin's Disease and Chronic Lymphocytic Leukemia

These tumors respond to the administration of nitrogen mustard (HN2), folic acid antagonists, such as aminopterin, amethopterin, and aminoanfol (4-aminopteroylaspartic acid), to triethylenemelamine (TEM) in doses from 1 to 6 mg. by mouth daily for a short period of time, to be followed by smaller doses less frequently; to related compounds such as triethylenephosphoramide (TEPA), to ACTH and cortisone; and to irradiation.

Chronic myelocytic leukemia may respond to the action of urethane or TEM and total care.

The treatment of choice of members of the lymphoma group, including chronic leukemia and Hodgkin's disease, must depend upon the biological behavior of the particular tumor in the patient under treatment and upon the physician's preference, which will be conditioned by his experience with the newer forms of chemotherapy.

Conclusions

The lymphoma group and particularly acute leukemia have responded to a more marked degree than any other form of cancer in early life to the new chemicals that have been developed within the last few years. Prolongation of life, amelioration of symptoms, and a return to a far happier and even a normal life for weeks and many months have been produced by their use. THESE AGENTS HAVE PRODUCED NO CURES. Their use, however, has opened a new era in the treatment of cancer, and has pointed the direction for future research. This direction is all the more important because of the lack of knowledge concerning the cause or means of prevention of acute leukemia and other members of the lymphoma group of tumors in infancy and childhood.

References

The most complete discussion of the results of the treatment of children with acute leukemia in many clinics in this country and Canada can be found in the following references:

1. *Farber, S.*, Ed.: *Proceedings of the Second Conference on Folic Acid Antagonists in the Treatment of Leukemia. Blood 7 (Suppl.): 97-190, 1952.*
2. *Mote, J. R.*, Ed.: *Proceedings of the Second Clinical ACTH Conference. Philadelphia. The Blakiston Co., 1951; Vol. 2, pp. 226-234; 251-288.*

Clinical instinct is the power of arriving without a conscious logical process at a definite conclusion, and is often possessed in a high degree by old nurses who know, but cannot give their reasons, whether a patient is going to recover or die, and by practitioners of long experience who similarly cannot explain the steps by which they reach a diagnosis and prognosis. . . . Sir Humphry Rolleston (1862-1944).

The Office Treatment of Hemangioma

Oliver Moore, M.D.

Hemangioma is a tumor of blood-vessel origin that may be clinically divided into the following classifications: capillary, cavernous, hypertrophic, and port wine stain.

The first three of these may be progressive and locally destructive and thus require treatment. It is well known that many of these lesions will undergo spontaneous regression and, when located upon areas such as the trunk or extremities, observation only is safe. However, as a hemangioma when small is usually readily controllable by simple innocuous means, it seems most reasonable to treat them as soon as they are seen, regardless of the age of the patient.

The treatment methods suggested here have been found to be effective, simple, and safe, and one need not fear future disabilities because of tissue damage and interference with growth, nor is hospitalization or expensive equipment required.

Classifications

The nevus vinosus (port-wine stain, birthmark) is a simple telangiectasis of venous capillaries that does not progress after birth. Aggressive treatment is not indicated, since little can be gained without producing scarring as undesirable as the original blemish.

Spider hemangioma is so named because of its appearance. There is a red, raised, punctuate, central "body" seldom more than a few millimeters in diameter from which small, dilated, serpiginous, capillary channels radiate, somewhat resembling the appendages of a spider. As the lesion is small and seldom a problem cosmetically, it is usually unnecessary to treat this lesion.

Capillary hemangioma (plexiform) occurs in the face, especially about the embryonal fissures of the neck, cheek, lip and eyelids. Raised, red, warty projections upon the skin are seen. Underlying muscle and bone may be involved producing local destruction. The tumor is compressible and contains little solid tissues, and consists of dilated capillary vessels filled with blood. There is little supporting tissue and the vessel walls are extremely thin.

The cavernous hemangioma formed of dilated channels with thin walls may have well-defined borders or be diffuse. The color is deep red or purple when the skin is involved, while deeper-lying tumors produce only a faint blush in the overlying skin. The tumor is compressible, may pulsate, produce an audible bruit, and be erectile. These tumors may attain a large size and are frequently multiple. The course is usually slowly progressive, the growth occurring as a result of formation of new vessels as well as by dilatation of the existing channels by the pressure of the blood. Spontaneous regression is common.

Hemangioma hypertrophicum is practically a solid tumor, only slightly compressible and formed by vessels of small lumen and greatly thickened walls. Pure tumors of this type are progressive, and, if very cellular, may be locally malignant. Treatment with sclerosing agents is generally unsuccessful and surgical excision may be necessary for eradication.

Materials

The materials required for the office treatment of hemangioma are simple and inexpensive. For the injection of a

From Memorial Center for Cancer and Allied Diseases, New York, New York.

Figure 1

sclerosing agent, the physician's office will usually supply all the necessary equipment. Figure 1 is a photograph of the treatment tray containing the following items:

1. Small syringe (in this case, a 2-cc. tuberculin syringe).
2. Suitable needles.
3. Gauze for preparing the skin and applying pressure following injection.
4. Small vial of sclerosing agent. Sodium morrhuate has proved satisfactory.
5. Alcoholic solution for cleansing the skin.

For the use of solid carbon dioxide, one must have the "dry ice" and a means of shaping it to cover the area to be treated accurately. Dry ice is available at almost any place where ice cream is sold.

Figure 2

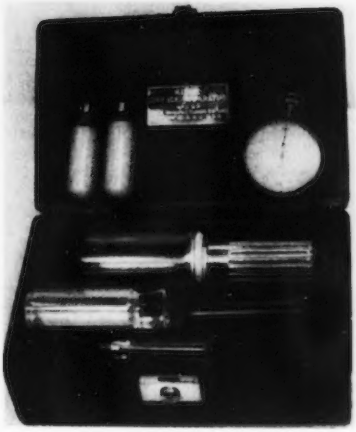


Figure 3

Figure 2 shows, on a small board, a chisel, hammer, and metal spatula to shape the ice. Gauze is needed to protect the fingers when the piece is shaped. A stop watch for accurate timing is a necessity.

Figure 3 is a photograph of a Kidde carbon dioxide set that provides small pieces of solid carbon dioxide as required.

Methods of Treatment

A hemangioma may be controlled by obliterating the lumen of the vessels making up the tumor. As previously mentioned, this process may occur spontaneously or upon initiation of rather slight trauma, and the process of obliteration may go on spontaneously. Treatment methods are designed to take advantage of the histological pattern and natural history of hemangiomas. Simple and harmless measures should be chosen.

Sclerosing-Therapy Technique. Varying types of sclerosing agents ranging from boiling water to soap solutions have been used. Sodium morrhuate has proved satisfactory and safe. The le-

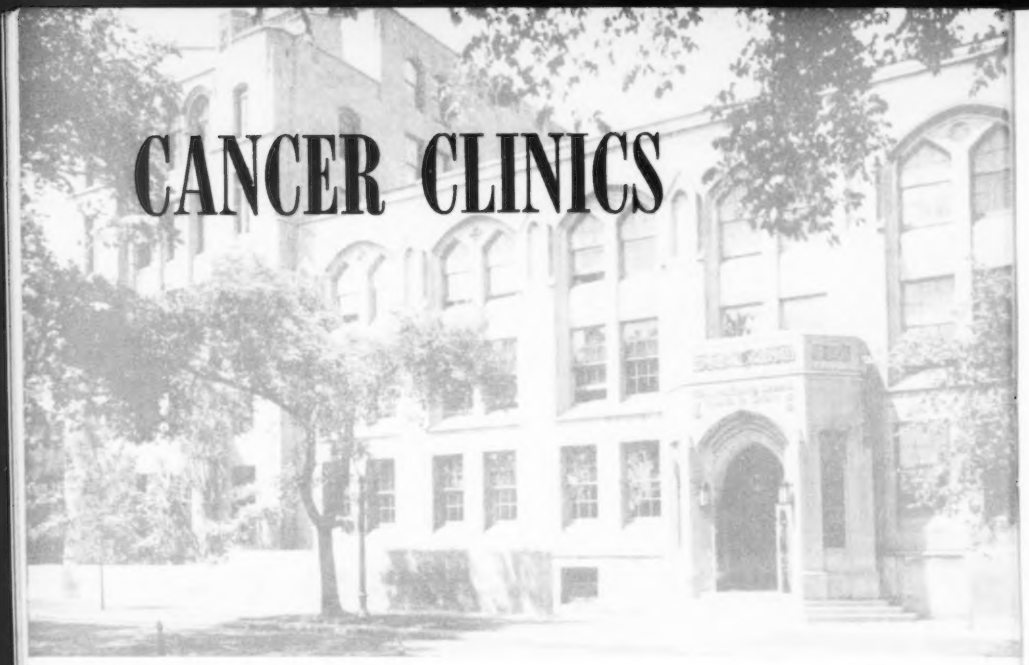
sion to be treated and the surrounding skin are cleaned with an antiseptic solution. A small needle (usually a 24 or 25 gauge) is inserted into the tumor and the sclerosing solution is injected as the needle is kept moving through the tumor. The sclerosing agent is kept away from the surface to avoid ulceration. Upon completion of the injection, firm pressure is made over the lesion for five minutes. When repeated treatments are required, the interval between treatments is usually one to three weeks, depending upon the tissue reaction. Usually about 1 cc. of sodium morrhuate is injected at a treatment but more or less may be used depending upon the size of the lesion. Hemangiomas that have most of their bulk beneath the skin surface and are thus not amenable to freezing with solid carbon dioxide are chosen for injection with sclerosing agents.

Technique of Freezing with Solid Carbon Dioxide. A piece of dry ice is obtained large enough to cover the area to be treated. This is shaped so that it exactly fits the lesion. The solid carbon dioxide is held firmly against the lesion and the treatment timed exactly by means of a stop watch. A sponge wrapped about the sides of the ice will protect the fingers. The choice of time of the treatment and pressure to be applied are matters which require some experience. As an initial treatment, ten to fifteen seconds may be chosen. A blistering reaction should develop in about six to twelve hours and considerable local edema frequently follows. In three weeks, there has been recovery of the treated area. If ulceration or infection is present, the next treatment is delayed.

The mother should be instructed as to the expected reaction. The treated area is kept covered with petroleum jelly or a bland ointment. Twice a day, the surface should be gently cleansed with oil and the crusts removed. If the reaction is not intense enough, the treatment period should be increased. If there is ulceration, the time is decreased. Large tumors involving not only the skin but the deep tissues may require many treatments, both by sclerosing agents and solid carbon dioxide. Patience and persistence are rewarded. The chief problem is avoiding excessive zeal with subsequent scarring. It is well to remember that regression, once initiated, will usually go on spontaneously. Areas that show growth should receive special attention.

I recall a boy just eleven years of age who was a runaway from home, got into many difficulties, was in many courts and finally came before the Boston Juvenile Court. He was placed in a private school in a small town, where a general practitioner, in his medical examination, discovered symptoms of a tumor of the brain. The diagnosis proved correct, but it was too late. This boy should not have been considered a delinquent; his physical defect was only one of his handicaps. In remembering his neglect, I think of a little girl who was likewise considered merely a behavior problem, but whose parents did something about it. Her attitudes and conduct were rapidly wearing out the whole family. With the assistance of a skilled pediatrician, who noticed, I believe he said, the pigmentation of her eyes, she was thoroughly examined at the Children's Hospital, where it was discovered that she too had a tumor of the brain. Thereafter, her problem was understood, and she was placed under competent medical and psychiatric attention, away from her home; the parents were thus given an opportunity to care for the other children under normal circumstances, and the patient was prevented from unjustly being brought before the court at some later date. How much better it would have been if the boy's parents and community had also sought assistance to eliminate apparent delinquencies!

Connelly, J. J.: Children are not expendable. New England J. Med. 248:1, Jan. 1, 1953.



CANCER CLINICS

Children's Cancer Clinic

Malignant disease in children is a leading cause of death between the ages of 5 to 14 years, according to the mortality statistics of the United States for 1948. Since the antibiotic era more deaths in children's hospitals are due to malignant disease than to any other cause. Although the over-all percentage of cures of childhood cancer is as low as 5 to 10 per cent, a better figure can be obtained with some of the localized malignant conditions. Early diagnosis and prompt treatment of some of the most rapidly growing tumors, such as the neuroblastomas of the adrenals, the embryomas of the kidney, and the retinoblastomas, have resulted in permanent cures. It is of major importance for the early diagnosis of cancer in children to recognize that the common sites of malignant disease in children differ from those of the adult. In children, the central nervous system, the eye, the kidney and adrenals, the blood-forming organs, the bones, and the supporting connective tissues are most commonly involved. In the adult, the gastrointestinal tract, the mouth and neck, the genital organs, the lower urinary tract, the breast, and the skin are the common sites of origin; these are rarely the sites of cancer in children. The following case histories illustrate four of the more common types in children.

Case 1

DR. HELMUT SECKEL: B. W., a white girl, aged 3 years and 4 months, had been well and growing healthily until late in September, 1948, when she vomited and complained of rather severe abdominal cramps. At a doctor's advice she was put on paregoric and a light diet. For the next week she ate fairly well, complaining off and on of mild "stomach pains." She was allowed to play outside in the yard. There, on the afternoon of October 1, she climbed

By Staff Members of the Bobs Roberts Hospital, Department of Pediatrics, University of Chicago, Chicago, Illinois.

a fence and fell down a short distance, landing on her buttocks. Immediately afterward she began complaining of severe abdominal pain and vomited several times. Her complexion turned a grayish yellow. There was no fever; the last bowel movement had occurred two days prior.

On examination in the hospital she appeared very ill and pale, but afebrile. Significant findings centered about the abdomen. The liver was somewhat enlarged and there was a hard mass in the right lower quadrant measuring 6×3 in. The mass was tender to touch and was palpable on rectal examination. The hemoglobin was 8 gm. per 100 cc.; red cells, 3.04 million; and white cells, 13,900. Her blood pressure was 140/80. An initial diagnosis of appendiceal abscess was made and anti-infectious and antianemic treatment administered. During the next two days the first impression seemed confirmed when the temperature rose to 38.9° C. However, when the fever and abdominal irritation subsided, some doubts were felt as to the correctness of the diagnosis. Hydronephrosis, hepatic hemorrhage, and kidney tumor with metastases to the liver were thought of. An intravenous pyelogram showed an incompletely filled system of dilated calyxes in the right kidney, which was displaced downward and laterally. A lung roentgenogram was clear.

On October 12, 1948, the child was operated upon and a tumor mass was removed, measuring 12×16 cm. and weighing 494 gm. (with kidney). There was considerable blood loss during dissection and tissue exuded into the abdominal cavity from a break in the tumor capsule. The liver was normal. A microscopic diagnosis of embryoma of the kidney was made (so-called Wilms's tumor). Postoperative recovery was smooth. In spite of early intensive roentgen-ray therapy to the right abdomen and chest and a later attempt with nitrogen-mustard treatment, anemia, wasting, and metastases in the liver and lungs were observed during the following months. The child died on March 28, 1949. Permission for an autopsy was denied.

QUESTION: What was the underlying cause for the initial picture that simulated appendiceal abscess?

ANSWER: Most likely the capsule of the tumor burst and led to abdominal hemorrhage and irritation after the girl had fallen from the fence. The tumor proved to be friable at operation, too.

QUESTION: Is this alarming type of a presenting complaint at all common in embryoma of the kidney?

ANSWER: No. Typically, the onset is insidious. The most frequent presenting complaint is an abdominal tumor, palpated either by one of the parents or by a physician during a routine examination. Next in frequency is a complaint of abdominal pain, not uncommonly associated with some fever or vomiting. This was the situation faced by the physician who saw the child about one week before the fall from the fence. Least common are complaints of urinary frequency and findings of hematuria, weight loss and anemia.

QUESTION: At what age does a Wilms's tumor usually occur?

ANSWER: Malignant neoplasms of the kidney area—that is, in children, a Wilms's tumor, an adrenal sympathicoblastoma, or a cortical carcinoma—occur most frequently at less than the age of 5 years. This is the reason why in well-baby clinics and on routine examinations of young children the flanks should be explored with great care by bimanual palpation. Other malignant neoplasms such as retroperitoneal sarcoma and teratoma and the abdominal type of Hodgkin's disease may be discovered early by a careful exploration of the abdomen.

QUESTION: I noticed that the patient, in spite of being in a sort of abdominal shock, initially had a blood pressure of 140/80. What is the significance of that?

ANSWER: A considerable number of children with Wilms's tumor do show a high blood pressure. The cause may

be either a Goldblatt mechanism or the production of some hypertensive substance on the part of the kidney tumor. In the "endocrine tumors" mentioned above, noradrenaline or cortical hormone may raise the blood pressure.

QUESTION: What is the over-all outcome of therapy in children with Wilms's tumor?

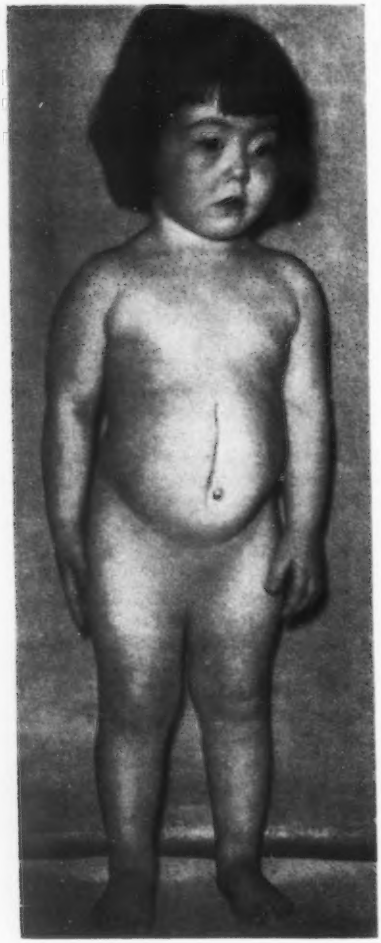


Figure 1. E. A., aged 2 years, 10 months. Note swelling of malar area.

ANSWER: With very careful surgical technique and intensive postoperative radiation of the abdomen and lungs the reported two- or more-year–survival rate of these patients approaches 25 per cent. Although this figure must be diluted by the large number of unreported fatalities, it serves to encourage the early search for and the radical treatment of malignant masses in the flanks and in the abdomen of infants and children.

Case 2

DR. PHILIP AMBUEL: The early history of the following case is available through the courtesy of Dr. Harold Dargeon of Memorial Hospital, New York City, who treated the child initially. The child's father is an army sergeant, and she migrated through several Army hospitals, and was referred to us in September, 1951, by one of our ex-residents who was then serving as a medical officer at Chanute Field.

E. A. is now 3½ years of age. When she was 3 months old an abdominal tumor was palpated for the first time, and when she was 5 months old she was taken to Memorial Hospital where an exploratory laparotomy revealed the presence of a large abdominal tumor with metastases in the liver. The mass was inoperable, and biopsy proved that it was a neuroblastoma. Following surgery, she was treated with nitrogen mustard, 2.8 mg. in one dose, followed by irradiation with 1000 kv. directed to the abdominal mass. The tumor receded, but, two months later, proptosis of both eyes and ecchymoses about the orbits revealed the presence of metastases in the skull. These new lesions were treated with 1000 kv. to the orbits. This therapy resulted in slight regression of the proptosis. In January, 1950, the course of HN2 was repeated and another 1000 kv. course of therapy was given to the abdomen. At this time the child appeared chronically ill; she was vomiting a great deal and having rather severe diarrhea. She received vigorous supportive therapy and showed some

temporary improvement, but in February, 1950, the proptosis and ecchymosis appeared again and a hard tumor mass was felt on the left mandible. Because of these new metastatic lesions, she was given a course of amethopterin consisting of 0.5 mg. intramuscularly daily from February 28 through March 3, 1950. This medicine produced a violent reaction with severe vomiting, considerable weight loss, and a sharp drop in hemoglobin to a level of 6 gm. Blood transfusions were used and after a short time the blood count became stable. However, the metastatic lesions continued to grow and new ones appeared in the skull. No further specific therapy or blood was given and during the last half of March, April, and May the metastases continued to grow and her general condition gradually deteriorated. The low point was reached the last part of May when she was severely anemic (Hb 3.3 gm.) and showed a marked enlargement of the liver, which then reached to the level of the umbilicus. In June of 1950, three months after treatment with nitrogen mustard, radiation, and aminopterin, and without any specific therapy or transfusions at that time, the child began to improve. By September, the liver was no longer palpable; the skull tumors were smaller, though still present, and she had recovered from her anemia (Hb 12 gm.). From October 1950 to September 1951, when she was referred to us, she was treated with intermittent courses of aminopterin or amethopterin, for periods of ten days, at intervals of about six to ten weeks. These courses of the folic acid–antagonist drugs were tolerated fairly well, although nausea, vomiting, and a tendency to diarrhea were encountered. During all of this time her general condition was fairly good, although the skull tumors were constantly present, and she continued to show an anemia at times, which required blood transfusions.

When first seen at Bobs Roberts Hospital in September 1951, her age was 2 years and 4 months, weight 27½ lb.

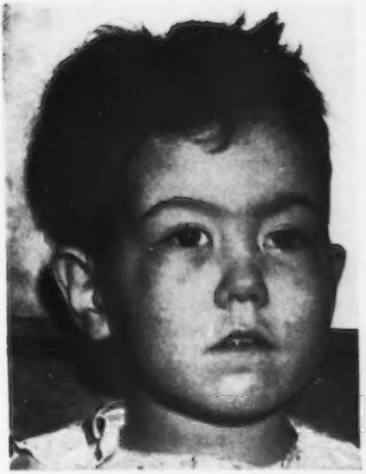


Figure 2. E. A., aged 3 years, 9 months.

and height 37 in., which was normal for her age. Her general nutrition and color was good. A bony tumor, 3 cm. in diameter, was palpated over the right frontal bone and irregular hard masses were present on both malar bones. Ecchymoses discolored the eyelids and the sclerae, and the conjunctivas were edematous and reddened. The fundi showed bilateral optic atrophy; there were no retinal hemorrhages. The submandibular lymph nodes were palpable but there was no other significant lymphadenopathy. The liver was enlarged and hard and the lower border extended 4 cm. below the costal margin. No other masses were palpated in the abdomen.

Blood studies revealed a hemoglobin of 10.7 gm.; a red-cell count of 4.18 million; white-cell count of 12,600; platelet count of 398,000; and a normal differential. The bone marrow was normal and no tumor cells were seen.

A roentgenogram of the skull showed an area of decreased density at the midportion of the right half of the coronal suture. The sella turcica was a little larger than normal. The optic foramina

were normal. Survey of the arms, legs, trunk, and spine showed no abnormalities. The bone age was normal. The chest roentgenogram was negative. The flat plate of the abdomen showed bilateral calcification in the region of the adrenal glands. On this admission the child was treated with P^{32}. She received an oral dose of approximately 300 microcuries per day for eight days with a total dose of 2440 microcuries. This first course was from October 6th to October 13th. Additional P^{32} in the same dosage was administered on October 23d, 24th, and 25th and again on November 21st to 24th inclusive. She tolerated this medication without ill effects and her blood counts remained normal. The child's general condition continued essentially unchanged and in January, 1952, she had her 4th course of P^{32} without ill effects. By May the malar tumors were enlarging again and a course of aminopterin, 0.5 mg. daily, was given. On the ninth day after the drug was started, she developed signs of severe toxicity with diarrhea, melena, and a toxic leukopenia and pancytopenia indicative of aplasia of the bone marrow. She recovered from this reaction after vigorous transfusion therapy, and there was no further growth of the skull metastases until August. At this time, a course of local irradiation was given to the anterior part of the skull, using a total dose of 1300 r. Since September, 1952, she has done well. She has no pain, is active and happy, walks normally, and is growing well. Her vision is impaired, and her speech is retarded. She has no gross hearing defect. At the time of her last visit, she was coming down with chicken-pox. She recovered from this without serious sequelae, but the tumor in the facial bones had enlarged and another course of radiation is planned in the near future.

In summary, this case illustrates a three-year survival after the recognition of an inoperable neuroblastoma of the adrenal, that had metastasized to the liver at the time of operation. The initial course of radiation and nitrogen mustard controlled the growth of the original tumor and the folic acid–antagonist drugs and local irradiation have controlled to some extent at least the skull metastases.

QUESTION: Is it not remarkable that other bones have not been invaded?

ANSWER: Very remarkable indeed. One must assume that this danger still exists as long as any metastasis is present.

QUESTION: What is the ultimate outlook for this child?

ANSWER: The neuroblastoma is one tumor that may become benign after it has once been malignant. One can hope that a cure can be achieved, if the local metastases continue to respond to treatment.

Case 3

DR. MILA PIERCE: J. M., age 4 years, had been a well child in every way until the age of 3 years, except for occasional attacks of tonsillitis; one attack was severe enough to require hospitalization for three days, at the age of 1 year; this and other attacks had responded well to antibiotic therapy.

In November, 1951, there was a change in her general health. About the first of the month she had an attack of vomiting that persisted twenty-four hours and was thought to be an epidemic gastrointestinal disturbance. Two weeks later, she suddenly ran a fever of 105° F. and had signs of a severe pharyngitis; she was treated with penicillin and the infection was controlled readily. At this time, although she appeared unusually pale, a blood count revealed no anemia or other abnormality of the blood. She continued to appear somewhat under par and about December 15th she again ran a fever, which then failed to respond to the usual treatment. Her physician noted an enlargement of the glands of the neck and an increasing pallor. A blood count confirmed the suspicion of anemia and revealed the presence of atypical white

cells. Her attending physician was alert to the possible diagnosis of leukemia and she was referred to Bobs Roberts Hospital where this diagnosis was confirmed by an examination of the bone marrow. At this time her physical findings were minimal; aside from pallor, a tendency to bruise easily, and some enlargement of the glands of the neck, the findings typical of leukemia were limited to the blood and bone marrow. The blood findings revealed a severe anemia: hemoglobin, 5.1 gm.; red cells, 2.04 million; a moderate leukocytosis of 11,250, with 3 per cent neutrophils, 30 per cent small lymphocytes, and 67 per cent blasts; a thrombocytopenia with a platelet count of 40,000 and an absence of reticulocytes. The bone-marrow smears indicated that 90 per cent of the cellular elements of the marrow were blasts of the stem-cell type.

Treatment consisted of a transfusion of whole blood to correct the anemia and of adrenocortical hormone; 10 units of ACTH was given intramuscularly four times daily from December 22d to January 15th, and 15 units four times a day until January 29th. The effect of the hormone therapy on the blood was indicated by a prompt fall in the total leukocyte count to a leukopenic level of about 1500, and a fall in the percentage of blasts. By January 7th the white-cell count was 1300, the percentage of neutrophils had risen to 23 per cent, blasts were absent from the blood, but the platelet count was still only 15,000; the anemia was again severe: the hemoglobin, 7.5 gm. and the red-cell count, 2,400,000. By January 10th the reticulocyte and platelet counts began to rise and by January 25th the blood findings were: hemoglobin, 12.7 gm.; red-cell count, 4,590,000; white-cell count, 5900; platelets, 291,000; reticulocytes, 6.4 per cent; neutrophils, 60 per cent; lymphocytes, 34 per cent; monocytes, 6 per cent; blasts, none. Her clinical improvement paralleled the improvement in the hematological findings. However, since the examination of the bone marrow on January 28th showed that 30 per cent blasts remained in the marrow, treatment was continued with cortisone. By February 14th, her clinical condition was good; there were no signs of anemia, or of purpura, and no lymphadenopathy, splenomegaly, or bone pain. Her blood findings indicated that the leukemic process was gaining momentum: hemoglobin, 11 gm.; red-cell count, 3,990,000; white-cell count, 5500; with neutrophils, 68 per cent; lymphocytes, 29 per cent; monocytes, 1 per cent; blasts, 28 per cent; and platelet count, 118,000. Treatment with aminopterin, 0.5 mg. daily, was started. This was tolerated well, without signs of toxicity such as stomatitis or leukopenia. It was continued for twelve days, when a complete remission had been obtained: hemoglobin, 10.5 gm.; red-cell count, 3,970,000; white-cell count, 5900; with neutrophils, 60 per cent; lymphocytes, 37 per cent; monocytes, 3 per cent; blasts, none; platelet count, 203,000; reticulocytes, 10 per cent. The bone-marrow findings showed only normal granulocytic and erythrocytic elements and a normal percentage of megakaryocytes.

She continued in good general health and in a hematological remission throughout the summer, but on September 4th, at the time of her routine examination, the spleen was noticeably enlarged. The leukocyte count was 22,700 and the blasts were again present in the blood smears. Treatment with aminopterin was started but this was tolerated poorly. After a few days she complained of abdominal pain and developed signs of a stomatitis. The drug was withdrawn, and she was admitted to the hospital again from September 9th to September 29th for a second course of ACTH therapy. Her symptoms of discomfort improved and the enlargement of the liver and spleen receded, but complete control was not obtained with ACTH. Aminopterin was again added on November 7th, but in spite of combined therapy with ACTH and aminopterin there were increasing

complaints of pain in her legs and feet so that she refused to walk. During the month of December she was very uncomfortable, with a severe anemia, tendency to bruise, and severe pain in her back and legs with every movement. It seemed evident at this time that, in spite supportative treatment with transfusions and antibiotics, a reversal of the leukemic process could not be obtained with the drugs that had been previously effective.

On January 17th, a new compound that had been under test at the Sloan-Kettering Institute, New York City, for treatment of leukemia in children who had become resistant to the adrenocortical hormones and the folic acid–antagonist drugs was made available to us. This compound is still in the experimental stage and is available only to research investigators at the present time, so that the details of dosage will be omitted from this report. Therapy was started with this compound on January 17th, when the clinical findings were those of a chronically ill child complaining of pain in the bones of the legs, marked splenomegaly and hepatomegaly, and multiple skin ecchymoses; the blood findings were: hemoglobin, 7.4 gm.; red-cell count, 2.74 million; white-cell count, 1240; platelets, 19,000; reticulocytes, 0.2 per cent; neutrophils, 28 per cent; lymphocytes, 61 per cent; and blasts, 5 per cent. After nineteen days of therapy, a reticulocyte count of 2.7 per cent was noted, and within the next few days it rose to 9 per cent. This was followed by a rise in the platelet, the erythrocyte, and the hemoglobin levels. The leukocyte count remained in the leukopenic range but blasts disappeared from the blood on February 7th and have not appeared again. Her clinical condition improved with the onset of the remission, the hepatomegaly and splenomegaly receded, and she is now beginning to walk. On March 2d the blood findings were: hemoglobin, 9.0 gm.; red-cell count, 3.00 million; platelets, 135,000; reticulocytes, 4.0 per cent; neutrophils, 34 per cent; lymphocytes, 64 per cent, and blasts, 1 per cent.

This case report illustrates the kind of control that can now be attained in the management of leukemia in children by the combined use of modern therapeutic agents that were not available so short a time as five years ago. The average life span of a child with leukemia in the preantibiotic era was about three months. This child has had the disease now for fifteen months, she has spent a total of sixty days in the hospital, received eight blood transfusions, and has been treated with three different types of anti-leukemic drugs. Although no drug is available that offers a hope of a cure at the present time, such a case record represents progress in the clinical management of the disease.

QUESTION: How many children will respond as well as this one?

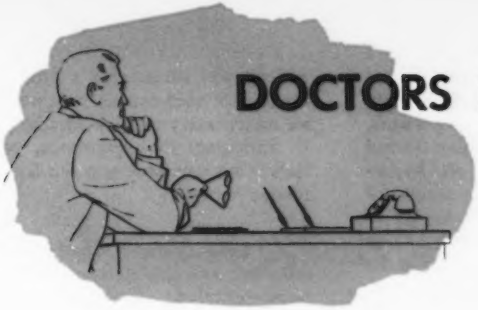
ANSWER: About a quarter of the cases treated. Some 20 per cent fail to respond to any kind of therapy and, of the 80 per cent who do go into a remission, about 25 per cent are now surviving longer than nine months and some as long as eighteen to twenty-four months.

QUESTION: Do you feel that repeated bone-marrow examinations are necessary for clinical management of the disease?

ANSWER: For the best control, yes. A clinical remission will not hold unless the marrow pattern has reverted to normal; if this has not happened the addition of another drug may complete a partial remission and give the patient several weeks of comfort.

QUESTION: In your experience, what are the conditions most commonly confused with an early leukemia.

ANSWER: I think it would be safe to say that about one third are misdiagnosed as rheumatic fever because of the unexplained fever, bone pain, and progressive anemia. Rheumatoid arthritis, lupus erythematosis, fever of unknown origin, and other malignant disease are also common referring diagnoses.



DOCTORS DILEMMAS

Q *Several persons who have read warnings that overexposure to sunlight is an inciting factor in the development of skin cancer have asked for specific advice concerning the possibility of skin cancer being caused by the use of sunlamps. Just where can the line be drawn?*

A Sunlamps produce ultraviolet light and there is good evidence that the penetrating rays of ultraviolet light favor the development of cancer, particularly in the skins of persons with light or sandy complexions, who do not tan readily. One should certainly caution such persons against the protracted use of sunlamps, except when specifically prescribed to alleviate a particular complaint, in which cases, of course, treatment is individually planned and discontinued when no longer indicated.

Q *A patient whom I have followed for several years has recently developed ascites. He does not have heart disease. Studies of liver function are within normal limits and roentgenograms of the gastrointestinal tract, gallbladder, and kidneys have failed to show any abnormality. What other studies can I order to determine the cause of this man's ascites?*

A You have apparently ruled out liver disease, congestive failure, and the obvious possible cancers. However, carcinomatosis must still be carefully considered as a possible cause of the ascites. Fluid should be removed and studied by both cell-block and Papanicolaou techniques for cancer cells. At the same time culture and guinea-pig inoculations should be done. Re-examination of the abdomen after removal of fluid may disclose hepatomegaly or metastatic nodules elsewhere in the peritoneal cavity. If these studies are unrevealing, peritoneoscopy should be considered when the abdominal fluid is relatively clear and not bloody.

Q *I have been following a patient, now 46 years old, who had a radical mastectomy for breast cancer nine years ago. Recently she has developed evidence of an expanding right-sided intracranial lesion, with paresis of the left side, hyperactive reflexes, and evidence of mild papilledema. She has had skeletal roentgenograms and a chest film and alkaline phosphatase determination. So far as we can tell, there is no evidence of recurrent disease in any other part of the body. Is craniotomy indicated?*

A Yes. The patient may have developed a new primary tumor or may have a solitary metastasis to the meninges or cerebrum. If the former, craniotomy and exploration are essential, and, if the latter, significant extension of life in good health may follow removal of a single brain metastasis.

Q *I have seen CA in my doctor's office and have read that radioactive substances can initiate cancerous growths. I am 35 years old and have been treated for rheumatic heart disease and hyperthyroidism. My doctor now suggests I have treatment with radioactive iodine for my hyperactive thyroid. Will this treatment make me sterile? Will it make me more susceptible to the development of cancer?*

A There is no evidence that radioactive iodine as used in the treatment of hyperthyroidism will result in sterility. Neither will such treatment stimulate the development of cancer in another part of the body.
[Ed. Note. The patient has received an answer to her inquiry, since we do not assume she is a "Constant Reader." The question seemed interesting and so is included here.]

Q *Approximately what is the interval between industrial exposure to arsenic with consequent arsenic dermatitis, and the development of skin cancer, should it ensue as a result of the exposure? A patient whose arsenic dermatitis followed after exposure during the manufacture of an insecticide and regressed reasonably promptly following a change of jobs is, I believe, excessively anxious about the possibility of related skin cancers developing in the future.*

A Skin cancer that can be directly attributed to exposure to arsenic is not frequently reported, possibly because of the long interval involved and faulty histories available. W. C. Hueper (National Cancer Institute) states that the average latent period between occupational exposure to arsenic and the appearance of skin cancer is about twenty-five years, with a range of from four to forty-six years. In most instances, a long exposure to the carcinogen and a long latent period exist before cancer is manifest. While a careful occupational history will often give a clue to the etiology of skin cancer, it is, of course, an unnecessary anxiety for the patient to anticipate its appearance, particularly if his exposure was not for an extended period.

Q *I have a patient, now 18 years old, who was operated on ten years ago for hypernephroma. A routine chest roentgenogram now reveals a solitary nodular circular density in the right lung, 3 cm. in diameter. The patient is completely asymptomatic. Should he have treatment with roentgen rays, or surgery, or is observation over a reasonable period of time indicated?*

A Experience has proved it is definitely worth-while to remove solitary metastases to the lungs. Tomograms should be obtained, and bone survey should be done to rule out other disease prior to surgery. Long survivals following removal of such single lung metastases as here described are not uncommon.

Q *Is a trial of HN2 suggested for a 55-year-old man with advanced, inoperable lung cancer, apparently radioresistant? The patient has symptoms of superior vena cava compression.*

A Yes; 0.1 mg. per Kg. of body weight of nitrogen mustard (HN2) for four successive days will frequently produce marked symptomatic improvement in patients with advanced lung cancer, including relief from pain, fever, night sweats, weakness, anorexia, chest pain, cough, and dyspnea. Objective improvement, as evidenced by weight gain, resorption of pleural fluid, improvement or disappearance of atelectasis, and relief of compression of superior vena cava may be expected in a smaller percentage of patients. A few individuals so treated respond so well to nitrogen mustard that definitive roentgen-ray therapy becomes possible.

new developments in cancer

Inhibition of Carcinogenesis by Hypophysectomy . . .

Evans and associates at the University of California have inhibited carcinogenesis by hypophysectomy two weeks previous to implantation of methylcholanthrene pellets into the gastrocnemius muscle of rats. Twelve of fifteen intact control rats developed palpable increase in connective tissue at the site of implantation and eight of these developed rapidly growing tumors in 200 to 300 days following implantation, while only one of fifteen hypophysectomized rats developed sarcoma at the site of methylcholanthrene implantation.

Still More Powerful Betatron . . .

The first 24-million electron volt betatron designed specifically for cancer treatment was recently displayed at the dedication ceremonies of the Andre and Bella Meyer Physiology Laboratory of Memorial Center for Cancer and Allied Diseases. This betatron is twelve times more powerful than the most powerful conventional x-ray machine and is housed in a specially constructed and protective structure with walls of concrete weighing 3500 pounds per cubic yard. The machine is 14 feet high, weighs 5 tons, and is bolted to a concrete wall five feet thick. Incidentally, the ground floor of the laboratory affords ideal bomb shelter and has been constructed with this in mind.

Antineoplastic Effects of Viruses . . .

West Nile virus, Ilhéus virus, Bunyamwera virus, and Egypt 101 virus have been shown by Southam and others at Memorial Center for Cancer and Allied Diseases, New York, to localize in certain neoplastic tissues. Although Egypt 101 virus has not given curative effects, the virus did appear to have a transient inhibitory effect on tumor growth in four and possibly nine of twenty-seven persons in whom infection was definitely established. There was evidence that the virus localized in tumor tissue, concentrating preferentially there as contrasted to normal tissues.

Survey of Diagnostic Delay . . .

Scheffey (Jefferson Medical College, Philadelphia) reported to the First Annual Clinical Meeting of the American Academy of Obstetrics and Gynecology, in Chicago, December 16, 1952, a

seven-year survey of the Philadelphia Committee for the Study of Pelvic Cancer, showing a 55 per cent combined patient delay and a 33 per cent combined physician delay in diagnosis and management of pelvic neoplastic disease. He considered this result sufficient evidence of need for similar surveys in other communities.

Cholesterol Synthesis . . .

Of interest to investigators of heart and circulatory conditions was Bucher's (Massachusetts General) finding that cholesterol can be synthesized by cell homogenates. Her proof that intact cells are not needed to produce cholesterol may inspire a rush to isolate the enzyme or other systems involved. The reward may be a measure of control of cholesterol synthesis in atherosclerosis, coronary thromboses, and other diseases. Bucher accidentally stumbled on the finding. She used liver-cell homogenates as a control to test the synthetic properties of liver cells that she had separated—and was surprised to find that the homogenates produced cholesterol as well as or better than whole cells.

Cobalt^{60} . . .

The cobalt teletherapy unit or so-called bomb provides a source of radiation similar to that of a 3 million volt x-ray machine. Compared with conventional 200 to 250 kv. roentgen rays, the advantages are higher depth dose, lower skin dose (since maximum ionization occurs about 0.5 cm. below the skin), relatively less absorption in bone compared with soft tissue, and lower integral, or volume, dosage for the same tumor.

These advantages do not justify a claim that cobalt may be the cure of cancer. Although it is an improvement over conventional roentgen-ray therapy, there is no reason to believe that the cobalt gamma rays are more effective than 3 mv. x-rays. Owing to lack of space in the atomic piles, where cobalt^{60} is produced, it will not be readily available for several years.

While psychologic understanding cannot affect the course of a cancer, we believe that it can be of practical value in dealing with many of the patient's problems. If one knows what the cancer means to the patient, in terms of fantasy and emotional import, it is possible to answer questions more satisfactorily and to decide how much to tell the patient and what topics to avoid. Furthermore, one can often be of considerable assistance in discussing the patient's illness with family members, making the inevitable disruption of family relationships more tolerable. By functioning in a non-rejecting, supportive role, the physician may add considerably to the patient's emotional comfort during the remaining months or years of life.—Stanley Cobb in The emotional significance of cancer: Psychiatric Conference. *Am. Practitioner* 2:261, March, 1951.

than the ordinary forty-eight chromosomes. And cancer cells -- all of them studied so far -- have shown enormous variation both as regards ploidy and chromosome fragments. As many as 1000 chromosome fragments were found in one cancer cell.

Albrink (Yale) now is conducting parallel experiments with Greene to measure the growth capacity of cancer, embryonic, benign tumor, and adult tissue. Greene, of course, continues to transplant tumors to the anterior chamber of the guinea pig's eye. If the transplant grows, it's highly malignant or embryonic, according to his findings. Albrink will grow explants in such nutrients as ordinary media, normal sera, and the patient's blood. If Albrink gets growth of a sample and Greene doesn't, he will give Greene bits of the culture-growing tissue for transplant to the anterior chamber.

Nicholas and Boell (Yale) are going all transplant enthusiasts one better. They have been implanting whole embryos in the anterior chamber of oxen eyes. The embryos usually develop for nine days. The technique, which enables the investigators to visualize incubation, is a highly satisfactory way of making enzyme and differentiation correlations.

Tartar (U. of Wash.) is constructing what amounts to man-made multicellular animals from protozoa. By delicate microsurgical techniques, he scars the sides of protozoa, causing them to clump together. Groups of about eighty have come together in this manner. The "animals" develop a "headness" and "tailness" of structure, and several areas of cells show differentiation similar to that found in multicellular forms.

Bonner (Cal. Tech.) has evolved at least a theoretical conception of how hormones act. He has shown that the most basic hormone, indole acetic acid, has positive and negative points for attachment to opposite charges on the protein molecule. The weed killer, 2-4-D, which essentially is a plant hormone, kills plants by attaching at one pole, positive or negative, thus blocking two-point attachment.

Lerner and Fitzpatrick (Ore.) have pretty well worked out various steps in the biosynthesis of melanin, and now they are attempting to clock it at a number of points with analogues. Potent in this process are the protein and steroid hormones. They consider melanoma so inevitably fatal that they are inclined to doubt that it ever has been

cured. Reported "cures," they feel, may be due to errors in diagnosis.

Marcus (Utah) has developed extremely sensitive methods of quantitatively determining hyaluronidase and anti-hyaluronidase concentrations. For at least the present, however, he does not intend applying the technique to cancer sera.

Dornfeld (Ore. State) has found that three of the four ribose nucleotides stop embryonic- and adult-tissue growth. These results and others -- Dunning (Miami) prevents or delays experimental tumors by feeding rats diets high in nucleic acids -- may presage increased chemotherapeutic investigation with nucleic acids and their components.

Rottino and others (St. Vincent's) have prepared about forty different antigens from the tissues of patients with Hodgkin's disease. They have been unsuccessful so far in producing specific antibodies for the disease.

Simpson and others (Detroit Institute for Cancer Research) are investigating the long-controversial contention that trauma sometimes may play a role in carcinogenesis.

COMING MEDICAL MEETINGS

Date	Association	City	Place
1953			
June 1-5	American Medical Association	New York City	Grand Central Palace
June 7-10	Northeastern Dental Society	Swampscott, Mass.	New Ocean House
June 10-13	American Proctologic Society	Boston	Statler
June 14-18	American Society of Medical Technologists	Louisville	Brown
June 15-19	Canadian Medical Association	Winnipeg	Royal Alexandra
July 14-25	International Congress of Radio-Biology	Copenhagen	
July 19-25	International Congress of Radiology	Copenhagen	
July 20-22	Postgraduate Medical Assembly South Texas	Houston	Shamrock
Aug. 10-14	National Medical Association	Nashville	Meharry Medical College
Aug. 24-29	World Conference on Medical Education	London	British Medical Assoc. House
Aug. 31-Sept. 3	American Hospital Association	San Francisco	Convention Hall
Aug. 31-Sept. 6	World Medical Association	Amsterdam	
Sept. 6-12	6th International Congress of Microbiology	Rome	
Sept. 9-12	Rocky Mountain Medical Conference	Salt Lake City	
Sept. 12-16	Washington State Medical Association	Seattle	Olympic
Sept. 14-17	International College of Surgeons	New York	Waldorf-Astoria
Sept. 15-20	Congress of the International Society of Surgery	Lisbon, Portugal	
Sept. 20-24	Pennsylvania State Medical Society	Pittsburgh	William Penn
Sept. 23-25	Michigan State Medical Society	Grand Rapids	Auditorium
Sept. 28-Oct. 1	American Dental Association	Cleveland	Auditorium
Sept. 29-Oct. 2	American Roentgen Ray Society	Cincinnati	Netherland Plaza
Oct. 5-9	American College of Surgeons	Chicago	Conrad Hilton
Oct. 11-17	National Gastroenterological Association	San Francisco	Biltmore
Oct. 12-16	American Society of Clinical Pathologists	Chicago	Drake
Oct. 26-30	American Cancer Society	New York City	Park-Sheraton

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